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Editorial

For some years, the Editorial Board of this JOURNAL has been concerned with what might be called the biometric handling of material submitted to it for publication. For this reason, it was the unanimous opinion of the Board that we should try to induce one of our members, namely, Professor Mainland, to undertake the task of preparing a series of articles dealing with the subject. But due to the pressure of work and, no doubt, some humility, he demurred for the time being.

The manuscripts are now in hand. They are divisible into three parts. The first is by way of an introduction, presenting "Questions for Use in Planning Investigations and in Evaluating Reports." As therein stated, "With change of tense from future to past, this series of questions becomes a scheme of the basic 'statistical' evaluation of a report of work already done. This is more fundamental than arithmetical tests; without it the arithmetic is meaningless and dangerous."

In addition, there are two further articles similarly entitled, "Notes on the Planning and Evaluation of Research, with Examples from Cardiovascular Investigations." It may be thought that each part is rather long, but it seemed desirable that the reader should be able to obtain something useful, and immediately usable, from each article, and not be left hanging in mid-air too long, as would happen if each article were made shorter and the whole divided into a larger series.

These are but a few words of explanation as to what prompted us and the author to formulate this series of articles as they now appear. Part I of this series appears in the present issue, and Parts II and III will be published in the June issue.

THE EDITOR

Notes on the Planning and Evaluation of Research, With Examples From Cardiovascular Investigations. Part I

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NATURE'S TRAPS FOR THE RESEARCH WORKER

To those of us who engage in medical research it often seems as if Nature were laying traps on every hand, to prevent our reaching the truth. Unfortunately, many of us discover these traps only when the product of months of painstaking work is refused publication because inadequate planning has led to ill-founded conclusions. Agencies that finance research are becoming increasingly aware of the need to scrutinize applicants' research plans, and this is one of the functions of a U.S. Public Health Service committee founded in 1956—The Advisory Committee on Epidemiology and Biometry. The experiences of that committee, of editorial boards, and of research consultants, reveal how widespread is the need for some systematic method of detecting and avoiding Nature's traps. The scheme offered here comprises ten sets of questions for use in planning an investigation and in evaluating research already performed, either one's own research or the reports of others' work. Explanatory notes accompany the questions, but where longer discussion of certain topics appears desirable it will be postponed for presentation in separate articles.

QUESTIONS FOR USE IN PLANNING INVESTIGATIONS AND IN EVALUATING REPORTS

With change of tense from future to past, this series of questions becomes a scheme for the basic "statistical" evaluation of a report on work already done. This is more fundamental than arithmetical tests; without it, the arithmetic is meaningless and dangerous. Only the investigators themselves can properly perform this basic analysis; but some of the questions may, in spite of the explanatory notes, necessitate consultation with a biometrician, or at least with someone who is acquainted with the concepts of experimenters' statistics. If the investigation comprises several experiments or surveys, the questions should be applied to each component separately.

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I. PURPOSE AND GENERAL METHOD

I-1. *What is the immediate purpose of our investigation? That is, what are the specific questions to be answered by it?*

I-2. *What is the more remote (more general or ultimate) purpose of our investigation?*

After answering the other questions in this series (I-X) we should return to Questions I-1 and I-2, and decide whether the investigation can give us the kind and amount of information that we need.

I-3. *Will the investigation be an experiment, in the strict sense?—A Survey?—Both?*

The two distinctive features of an experiment, in the strict sense, are as follows:

1. An investigator, wishing to compare the effects of two or more factors, assigns each of them *at will* to the individuals (e.g., human beings, animals, or batches of a chemical substance) that comprise his test material.

2. The investigator can assign the factors in such a way as to avoid bias—more accurately, to reduce the risk of bias to a predetermined degree (see especially Question V-3, below).

A piece of nonexperimental research is best called a "survey," if we remember that a survey can be conducted on as few as half a dozen subjects.

The amount of interference with, or manipulation of, our test material is not a criterion of experimentation. For example, an investigator wished to compare intravascular blood pressures in cardiac and noncardiac diseases. He inserted needles into the brachial arteries, catheters into the pulmonary arteries, and needles into the jugular bulbs. Since he had not assigned the factors under test (cardiac and noncardiac disease) to the subjects, he conducted a survey, just as if he had compared male and female statures. The importance of this apparently pedantic distinction will appear later.

The 109 articles that appeared as "Original Communications" in this JOURNAL during the first eight months of 1957, could be classified as follows: surveys, 75; experiments, 21; experiments and surveys in the same report, 3; other types (theoretical discussions, descriptions of technique, etc.), 10. Perhaps closer scrutiny would place more articles in the mixed (experiment and survey) class, but surveys were clearly in the majority, as they must be in clinical research. For example, we cannot, with rare exceptions (such as the common cold), inflict diseases on human subjects; nor can we hope to impose long-term dietary habits on one group and restrain our controls from those habits. If the factors under study are sex or age or occupation, or any other biological or environmental factor, we have to take the allocation to our test subjects that Nature or society has provided, each factor entangled with others.

I-4. *If the investigation is a survey, will it be anecdotal or statistical?*

Anecdotal surveys, merely recounting experiences and impressions, are not to be despised, any more than are the oral anecdotes of an experienced clinician. We benefit by knowing what *can* happen, even though we do not know how often it happens, or why it happens—for example: the survival for more than 57 years of three patients with congenital pulmonary valvular stenosis; unusual autopsy findings after cardiac surgery; a cardiologist's difficulties and errors in the interpretation of right-heart catheterization data. Many surveys that aim at being statistical would have value as anecdotal surveys if they would drop percentage frequencies, statistical tests, causal explanations, and attempts at generalization.

I-5. *If the investigation is a survey, will it be retrospective or prospective?*

Retrospective (backward-going) studies, in which we investigate phenomena that have already happened, form the commonest type of survey in everyday medical research. When they are used in a quest for etiology (e.g., the relation of dietary or smoking habits to disease), a serious source of bias is the knowledge (or even the conjecture) of the diagnosis by the patient or observer, or both. Prospective (forward-going or follow-up) studies are, however, not necessarily free from bias (see Section VII*).

I-6. *If the investigation is a survey, is there a hypothetical experiment which, if it were possible, we would perform instead of the survey?*

We should use this imaginary experiment in answering subsequent questions on surveys in this series. This is the best way of bringing to light the difficulties and uncertainties inherent in survey research, and of showing what we should try to achieve, as far as possible, in our survey methods.

In general terms, performing a simple experiment on two factors (A and B) we would randomly allocate our subjects to these factors (see Question V-3†), but otherwise treat the two groups alike, and we would account for all subjects at the end.

Our chief reference experiment in the notes that follow, to illustrate the features of a good study in a difficult field, will be a therapeutic trial conducted by the American Heart Association and the Medical Research Council of Great Britain,[1] and entitled "The Treatment of Acute Rheumatic Fever in Children. A Cooperative Clinical Trial of ACTH, Cortisone, and Aspirin."

II. THE POPULATION OR UNIVERSE

II-1. *What is the initial definition of our population or universe, i.e., the kind of subjects or material to be studied, and to which our conclusions will be applicable?*

Nearly all research aims at generalizing from a sample to subjects or material of like kind. Therefore, we must make very clear what we mean by "like kind," and that often requires a detailed description of our sample.

The Rheumatic Fever Trial investigators agreed upon five major manifestations of the disease (e.g., carditis, chorea) and five minor manifestations (e.g., fever, elevated sedimentation rate). They defined all criteria minutely, and they adopted certain rules regarding the numbers of these various manifestations requisite for a patient's admission to the study. This was the beginning of *systematic sampling*—a division of the total rheumatic fever population by certain defined characteristics into two parts, one of which, not meeting the criteria, was to be excluded.

Out initial definition will be implicitly supplemented and modified by our answers to subsequent questions regarding selection of subjects, methods and times of observation, auxiliary therapy during observation, and other features or phenomena.

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*Section VII of this series of questions will appear in a subsequent issue.

†Section V of this series of questions will appear in a subsequent issue.

For example, the Rheumatic Fever Trial report gives the locations of the centers where the study was conducted, and the exact dates (in 1951 and 1952) between which children were admitted to the study. The implications—racial, geographic, climatic (including seasonal) and socioeconomic—would have to be considered if, for instance, conflicting results were obtained from a similar trial conducted in Vladivostock or Nigeria. The dates of the experiment are important because we cannot assume that acute rheumatic fever will remain the same disease through several decades, or that ACTH preparations will not differ considerably in five years.

II-2. *What other populations are excluded by the definition given in response to Question II-1?*

Whenever we define and divide, we should ask: "What kinds are we excluding?" In the Rheumatic Fever Trial some early and mild cases would doubtless be excluded. So also, as the report points out, would "questionable cases where continued observation of patients may be necessary for definitive diagnosis."

II-3. *If all the available subjects of our chosen population are not to be investigated, how is the sample to be taken?*

II-4. *If the sample is not to be taken by a strictly automatic random process, how may the sampling method affect the definition of the population?*

If there are available more subjects of the class desired than we wish, or are able, to include in our investigation, we should, if possible, take our sample by a strictly random method (to be discussed in a subsequent article). Otherwise, we have no means of arguing numerically from our sample to the total available subjects in that class. Moreover, unless we take an automatic random sample, our original definition of the population must be supplemented by the criteria, often vague and perhaps bias-laden, by which we have made our selection.

III. SUBDIVISION OF POPULATION

III-1. *Why do we subdivide (stratify or systematically subsample) our population and test the factors under study (A, B, etc.) within each subsample or stratum?*

Systematic sampling goes far beyond an outline chart of territory to be explored (Question II-1). For example, the Rheumatic Fever Trial was conducted at 12 centers—6 in the United Kingdom, and 6 in the United States and Canada. At each center the patients were divided into two groups by age—0 to 15 years, 16 years and over; and into three groups by duration from onset of attack to start of therapy—14 days or less, 15 to 42 days, 43 days and over. Each center, therefore, provided six subgroups for the comparison of ACTH, cortisone, and aspirin within each subgroup. This procedure is so characteristic of experimentation, and of all good surveys, that discussion might seem superfluous; but in every investigation we should clearly recall its threefold purpose: (1) to reduce bias, (2) to reduce the effects of interclass variation, and (3) to obtain the advantage of equal samples.

Reduction of Bias.—The popular notion of bias as a psychologic phenomenon still lingers with some medical investigators. Bias is anything that makes a sample different from what it purports to be—it is *a mislabeling.* For example, if children and adults had been grouped together in the Rheumatic Fever Trial, an excess of children in, say, the aspirin group, as compared with the cortisone

group, might have produced a difference in outcome that was not due to any treatment difference at all, or it might have masked a real benefit due to one of the treatments. The true labels of the groups would have been "Aspirin (Many Children)" and "Cortisone (Few Children)." We should always ask: "What may our labels be hiding?"

Reduction of Effects of Interclass Variation.—The Rheumatic Fever Trial investigators could have balanced numerically, in the three treatment groups, the two age groups and the three duration-to-treatment groups, in order to prevent bias due to disproportionate numbers, but there would have remained the other danger from excessive interclass variation in response—reduction of sensitivity of the experiment. For example, cases treated early might have reacted in the same way to all three treatments, and thus have masked a real benefit conferred by one of the treatments on the cases treated later.

Advantage of Equal Samples.—The risks mentioned in the preceding two paragraphs could, of course, be avoided by allocating the three treatments without regard to age or duration of disease, and dividing the data into age-duration classes after the experiment was over; but then it might be found that one or two of the treatments had very few representatives in certain of the classes. This inequality does not introduce bias (provided that the allocation of patients to treatments has been strictly random—Question V-3), but for a given total number of subjects equal-sized treatment samples give us the most information, i.e., the greatest likelihood of detecting a treatment difference, if one exists.

III-2. *What, in the form of a list, are the factors (in addition to the factors under test) that affect, or could conceivably affect, the phenomena to be observed?*

III-3. *Which of the factors listed in answer to Question III-2 are to be used in subdivision of the population?*

III-4. *Why are the other factors listed in answer to Question III-2 not to be used in subdivision of the population?*

III-5. *Why are the subdivisions of the population not to be coarser or finer?*

Decisions regarding the extent of systematic sampling (Questions III-4 and III-5) should be based chiefly on four considerations:

1. Simplicity, clarity and objectivity of dividing lines. Potential users of our results should be able to classify our subjects as we have done.

2. The (known or presumed) relative weights of the factors—their power to produce differences in outcome, and thus cause variation and bias. In the Rheumatic Fever Trial this was probably the reason for subdivision by age but not by sex.

3. Feasibility and convenience. The Rheumatic Fever investigators could have subdivided the patients into many subclasses by various combinations of the major and minor manifestations used as criteria for admission to the trial. They could have divided ages by single years, and duration to treatment by 3-day intervals. Such a scheme would not only have been difficult to operate; it would have broken down because there would seldom have been found three children sufficiently alike in all particulars to go into any one subclass.

Sometimes it is argued that if we make the subdivision very fine and then discover that there is no "significant" difference in outcome between the sub-

classes, the data from the various subclasses can then be pooled. But with small samples (say, a dozen, or even more, in each subclass) significance tests often fail to detect real differences. The fault of this plan of fine subdivision—a very common fault in clinical and laboratory research—is that it tries to answer too many questions from the one investigation.

4. Usefulness in application of results. Before every investigation we should ask: "By whom, and under what conditions, will our results probably be used?" Fine distinctions between differences in response in different subclasses are often of no consequence in the practical application of the results of a clinical trial.

In summary, systematic subdivision should be carried, not as far as possible, but as far as is convenient and useful; and often a balance must be struck between these requirements.

III-6. *Are we going to make paired comparisons, i.e., within the same subject, or between subjects that are matched in some way? If so, why?*

The advantage of using a patient or animal as his own yardstick or control is well known, as is the use of litter mates; but unless there is such clear justification for pairing, it should be avoided. It is difficult to justify this warning without describing methods of analysis, which are different for matched pairs and group comparisons, but we can make the general statement that information is lost if pairing is used where it is inappropriate.

IV. SKELETON TABLES OF RESULTS

For convenient reference the factors under test can be symbolized by A, B, etc. These may be qualitative features (attributes or events) such as sex, diseases, different phenomena in the same disease, death or survival, location of residence. Or they may be measurements, such as ages or blood pressure levels.

The things to be observed (for possible effects of the factors under test) can be symbolized by X, Y, etc. These may also be qualitative features or measurements. (When there are only two classes the symbols X and not-X are often used.)

IV-1. *How, in skeleton form, will the results appear?*

Sometimes our aim is only *an estimate* of a particular population value, such as the proportion of patients, treated by a certain method (A), who show improvement (X) at the end of two years from the start of a therapy; or the mean and variation of plasma cholesterol levels (X, Y, etc.) in healthy subjects. More often, our purpose is *a comparison*—for example: the prevalence of rheumatic heart disease (X) in (A) native-born Floridians and in (B) immigrants to Florida; the incidence of complications (X) in patients subjected to (A) left-heart catheterization and those subjected to (B) angiocardiography through a needle in the left atrium; mean levels of plasma cholesterol (mean of $X + Y + Z$, etc.) in healthy males of different ages (A, B, C, etc.).

The report on the Rheumatic Fever Trial contains the two main types of data—counts of individuals (*enumeration data*) and measurements (*mensuration data*). It displays enumeration data as actual frequencies (numbers of individ-

uals), or, if it gives percentage frequencies, it supplies the total number in the group concerned; because *percentage frequencies without actual numbers are meaningless.*

A table containing all children who were without subcutaneous nodules at the start of therapy displays the development of nodules during therapy, under the following headings:

TREATMENT	DEVELOPED NODULES	DID NOT DEVELOP NODULES
ACTH Cortisone Aspirin		

This is a 2 × 3 association table, commonly called a *contingency table* because it displays the joint occurrence of two sets of events, attributes, or phenomena (cf. "contact," from the same Latin root). The simplest form of contingency table is, of course, the fourfold table—e.g., Treatments: A, B; Outcome: Died, Survived.

IV–2. *Are measurements to be presented as (a) mensuration data (e.g., as means or variations), or as (b) enumeration data (e.g., in contingency tables)? What will determine the choice between (a) and (b)?*

Some of the Rheumatic Fever Trial observations, such as temperature, pulse rate, sedimentation rate, heart size, and conduction time, were measurements, and therefore they could have been used to compare the treatment groups in terms of means, variation, and time trends of measurements. Instead, the report presents the data, derived by measurement, as enumeration data. For example, it displays the percentages of children who showed changes in the transverse cardiac diameter of 0.6 cm. or more, between the start of therapy and the end of the third week. The headings are: Increase in Diameter, Decrease in Diameter; ACTH, Cortisone, Aspirin. (Treatment-group totals are given, of course.)

Analysis of measurement data by merely "counting heads" sacrifices some information, and so makes the comparison of treatments less sensitive—less likely to reveal a small but real difference. Our tables and method of analysis must, therefore, depend on the exact question that we are asking. For instance, the mean change in cardiac diameter, from beginning of therapy to the end of the third week, might differ significantly between treatment groups for various causes, such as small changes in the same direction in many children, or large changes in a few. Obviously, the Rheumatic Fever Trial investigators did not consider a significant *mean* difference of practical importance. They wished to know whether significantly *more children* showed a change of over half a centimeter in one treatment group than in another.

By contrast, in a cancer chemotherapy trial a tiny fragment of evidence on tumor inhibition by a certain chemical might provide a useful suggestion for the synthesis of a related compound. The extraction of full information by analysis of actual measurements would, therefore, be desirable.

The dividing lines in a contingency table—e.g., 0.6 cm. for change in cardiac diameter; febrile, afebrile; bradycardia, normal pulse, tachycardia—must, of course, be drawn before the data are inspected.

The Rheumatic Fever Trial data were abundant, complex, and of diverse character. Therefore, the simplicity and clarity with which they are presented and analyzed should provide a salutary lesson when we are tempted to apply elaborate treatment to our data, including the production of complex expressions such as over-all indices of clinical improvement.

IV–3. *What do we expect to be the order of magnitude of the frequencies and measurements—e.g., percentage of X's in A's, means of measurements, variations between measurements?*

Such information is necessary before we can form any estimate of necessary sample sizes or likelihood of success in our search for differences, if real differences exist.

IV–4. *Are the sampling units correct?*

The units that composed the samples in the Rheumatic Fever Trial—the sampling units—were individual patients, and the randomization (Question V-3) assigned each of them *independently* to the treatment samples, just as cards in thorough shuffling have freedom to move independently. Each unit could then contribute to his treatment group an independent piece of information regarding the effect of the treatment tested on him. This requirement is fairly obvious, but many research workers are rather vague about their sampling units and the need for their independence.

Wrong Sampling Units.—Let us suppose that a dentist, having attended to the teeth of two boys, instructs one of them to use dentifrice A and the other to use dentifrice B (and insures by parental cooperation that his instructions are carried out). After a certain length of time he finds that the boy who used dentifrice A has 8 carious teeth, while the other boy has no caries. This is a "highly significant difference," but we require no profound knowledge of dentistry to appreciate that the caries difference provides quite insufficient evidence that the dentifrice difference was responsible. We know that persons differ in their tendency to develop caries; therefore, the individual teeth in any mouth do not provide independent pieces of information about the effect of a dentifrice. It is not teeth, but boys that are the sampling units, and therefore there is only one sampling unit in each of the A and B samples.

In this simple case the point is obvious; but it was not obvious to a distinguished worker in nutrition and dentistry who reported on the teeth of 5-year-old children in a certain city. In 1943, 30.1 per cent of 36,196 teeth were carious, whereas in 1945, 26.5 per cent of 13,381 teeth were carious. The difference, although small, was "very highly significant" because the samples were so large; but they were spuriously large. In 1943, the number of children was 1,870; in 1945, it was 691; therefore, each child must have contributed about twenty teeth. The investigator had measured over and over again the same tendency (or resistance) to caries, but in the analysis had counted each contribution as independent.

This error—the use of *wrong sampling units*—can be called also "spurious enlargement of samples," "spurious replication," or "counting the same thing over again." The simplest proper analysis in the above example would be a

comparison of the percentages of children with caries in the two groups, as was done elsewhere in the same report.

Choice of Sampling Units.—In deciding upon sampling units we should ask: "Of what population do we desire an estimate?" For example, if we have conducted aortography by femoral artery catheterization 86 times and have never produced cerebral complications, we may be impressed by the apparent safety of the method; but this figure does not give us an estimate of the risk run by *patients* subjected to the technique. We obtain such an estimate by noting that the 86 injections were performed in 18 patients, the number of injections ranging from 2 per patient up to 10 (in one patient). We can, therefore, assert that in 18 patients, each injected twice, no cerebral complications occurred, and we can make similar statements regarding fewer patients who received more injections. If we are inclined to argue that the risk of complications is independent of the patient—that the injection is the sampling unit—we should ask ourselves: "If we had performed the 86 injections in only one patient, would we be as confident about the lack of risk as we would be if we had performed one injection in each of 86 patients?"

Bilateral organs or parts, such as kidneys, right and left cardiac ventricles, easily lead to the use of wrong sampling units; and so do "episodes," such as epileptic seizures, myocardial infarction, and attacks of rheumatic fever.

Sampling Units in Measurement Data.—Laboratory workers, making and analyzing measurements, not infrequently fall into the same trap. If we made 500 readings of body weight on 50 men, weighing some of them once, some twice, some three times, and so on, the mean of the 500 readings would not be the mean weight of the 50 men, or an estimate of the population mean weight. Even if we weighed each man 10 times, the variation among the 500 readings would be a mixture of *inter*subject and *intra*subject variation (between the weights of the same men on different occasions). If we used this mixture (e.g., in the form of a standard deviation), we would be using wrong sampling units. If we wished to reduce the effect of intrasubject variation (or fluctuation), we ought to take the same number of readings per man, and average them for each man, to obtain 50 mean values. The mean of these 50, and the variation among them, would be estimates of the population mean and variation for men under the specified conditions (including number of readings per man).

All this is self-evident, but it is frequently forgotten in the laboratory. For example, by placing electrodes on the surface and in the subendocardium of dogs' ventricles we can study, by simultaneous electrocardiograms, the time relationships of the peaks of the two T waves. If we obtain 69 such time differences (surface *minus* subendocardium) from 11 dogs, then find the mean of the 69 readings and their variation (standard deviation), we have used the wrong sampling units—readings instead of dogs—and we have a mixture of interanimal and intra-animal variation. If a report gives the average or variation of N readings (or "experiments" or trials) on a total of M animals or human subjects, we should look for wrong sampling units. (We should wonder, also, about the possibility of selection or rejection of readings, and the possibility of bias-causing differences between the subjects.)

IV–5. *Are the denominators correct?*

Wrong Denominators.—The Rheumatic Fever Trial report shows that when the children who had chorea at the start of therapy were examined at the end of therapy (6 weeks later), 12 of them still had chorea: ACTH, 1; cortisone, 2; aspirin, 9. Expressing these figures as percentages of the 12 cases, we have: ACTH, 8.3; cortisone, 16.7; aspirin, 75.0. It appears that, compared with ACTH-treated children, the cortisone-treated children had twice the likelihood of remaining choreic, and that the aspirin-treated children had nine times the likelihood. The figures would be all the more impressive if, instead of 12 children, there had been twelve dozen, with the same percentages as above; but the inference is quite fallacious.

The Rheumatic Fever Trial investigators, of course, did not calculate these percentages, because we have used the *wrong denominator*—the total cases (12). If there were more aspirin-treated than ACTH-treated children, even if there were no difference in the effect of aspirin and ACTH, we would expect more choreic children in the aspirin-treated group. The proper denominators are the totals in the three groups at the start of therapy: ACTH, 9; cortisone, 19; aspirin, 26. These are the "total numbers exposed to risk," and at the end of therapy each total contained choreic (C) and nonchoreic (not-C) children.

Denominator for Incidence and Prevalence.—The prevalence of chorea at the end of therapy was, therefore, C/(C + not −C). The denominator comprises the numerator *plus* those who would have been in the numerator if they had been choreic at that time. If we started with nonchoreic children and recorded those who had developed chorea during the six weeks, even if they were not choreic at the end of that period, the *incidence* would be expressed by the same formula, but C would stand for the number of children who developed chorea.

In the three groups the prevalence of chorea at the end of therapy was: ACTH, 11.1 per cent; cortisone, 10.5 per cent; aspirin, 34.6 per cent. The first two groups have now almost identical figures, and, although the aspirin-treated group shows the highest prevalence, the contrast is much less than when we used the wrong denominator.

"Sex Incidence" and "Age Incidence".—The foregoing comments may seem needlessly elementary, but internationally famous medical investigators still fall into the trap, especially with regard to "sex incidence" and "age incidence." For "age incidence" a frequency table is often presented, and perhaps a graph, showing patients' ages on the horizontal axis and numbers of patients (or percentages, with total *patients* as denominator) on the vertical axis. Often the graph line rises at the earlier ages and falls at the later ages. Those who present such graphs seem to forget that this decline is exactly what they should expect, even if the incidence of the disease were uniform at all ages, because in the latter part of life there are progressively fewer persons alive. (The occurrence of any disease at the age of 150 years is zero!) Even the earlier rise may be partly an artifact, because a physician may have relatively few child patients.

The graph can be said to show "incidence (or prevalence) of ages" in the patients—part of the description of the sample, but of little further use. For the denominator in calculating incidence (or prevalence) of the disease at different

ages, we require the numbers (population) at risk at each age, i.e., the observed patients *plus* the persons who would have come to the particular physician or hospital if they had had the disease. Such denominators are usually unknown.

"*Average Age*".—Wrong denominators can be disguised in averages, as in statements like: "The average age of male patients admitted with myocardial attacks was X years," and "The average age of female patients was higher than that of males." To exaggerate and simplify, let us suppose that 100 males aged 50 were exposed to risk, the same number at age 60, that the incidence of myocardial attacks was 10 per cent in each group, and that all cases came to us. We should meet 10 at age 50 and 10 at age 60—average age = 55 years. For contrast, let us suppose that there were again 100 males at age 50, but only 20 at age 60, and that the incidence was again 10 per cent. We should meet 10 at age 50 and 2 at age 60—average age = 51.7 years. Male-female age comparisons are likewise influenced by numbers exposed to risk, by incidence, and by admission rates.

The "average age at death" still traps some workers. From autopsy or hospital records, or by following their patients for a number of years, they find the average (arithmetic mean) age at death *for the patients who have died.* Obviously, we cannot tell the mean age at death of a group of patients, say with myocardial infarcts, unless we wait until all of them are dead. We might seem to be on safer ground in comparing two groups (e.g., sexes or diseases) with respect to mean age at death, but we have no right to imagine that the error (of underestimation) will be the same in both averages.

What we are usually trying to reach by an average age at death is some indication of the life-shortening effect of a disease, and if we thought more carefully about our question, we would doubt whether the average age, even if derived from deaths of all patients, was a satisfactory answer, because that average depends both on age at onset and duration between onset and death.

If, however, we ask about the duration of life after we have first diagnosed the disease, and if the disease kills some patients before any are lost to follow-up, we can obtain an answer to our question. For example, we can say: "By the end of three years X per cent had died of the disease, Y per cent had died of other causes, and Z per cent were alive." Or, if we can follow all patients until half of them have died, we can state (in years) the median duration from diagnosis to death. Generalization will, of course, be risky unless we have enough patients to explore factors that may influence the median duration.

IV–6. *How may the structure of our measurements mislead us?*

The measurements that we analyze are often not the original, simple, direct measurements, but adjusted, derived, or complex measurements (e.g., ratios or indices), and they can lead us astray. Let us suppose, for example, that the mean systolic blood pressure rises by 0.8 mm. per annum—a linear relationship. If an investigator thought that the ratio of blood pressure to age would reveal something of importance, he might obtain the following figures:

Age (years)	20	30	40	50
Blood Pressure (mm.)	120	128	136	144
B. P./Age	6.0	4.3	3.4	2.9

The ratio (B.P./Age) diminishes with advancing age; but this is no new discovery. It is inherent in the original linear relationship between blood pressure and age.

At a certain stage in the analysis of the Rheumatic Fever Trial data certain differences appeared between the cortisone-treated and aspirin-treated children with respect to the lengths of the electrocardiographic P-R intervals. It was then realized that the physicians had followed the customary procedure of adjusting P-R intervals by pulse rate, and that, since cortisone and aspirin affect the pulse rate differently, the adjustment had built in an intertreatment difference in P-R intervals.* (The published report gives figures that are free from this effect.)

Even if we wish to use, in the end, adjusted, derived, or complex measurements, our rule should be: To avoid misinterpretation, first explore the relationships of the simple, unadjusted measurements.

I am much indebted to my colleague, Miss Lee Herrera, for constructive criticism of this and subsequent articles.

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*For this example I wish to thank Miss Marjorie T. Bellows, Chief Statistician, American Heart Association.

The Effect of Tilting on the Right Atrial Pressure of Patients With Heart Failure

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The first observations on the effect of postural changes on right atrial pressures were made by Stead, Warren, Merrill, and Brannon.[1] They noted that pressures in the right atrium ranged from 15 to 75 mm. of saline in recumbent normal patients, and, after 5 to 8 minutes of motionless standing, there was an average decrease of approximately 60 mm. of saline. Davis and Shock[2] reported a decrease of 50 to 60 mm. of saline in right atrial pressure when the body position of normal patients was changed from supine to a 45° sitting posture.

The effect of upright tilting on the right atrial pressures has been noted both in normal individuals and in patients with organic heart disease. Approximately two thirds of the latter group were in congestive failure. It is the purpose of this communication to report these observations.

MATERIAL AND METHODS

Twenty-seven subjects were studied, with repeat observations in 6, 5 following treatment of their congestive failure and 1 following a pericardectomy. The patients are listed in Table I, the diagnoses of heart disease and congestive failure being made by the usually accepted clinical criteria.

In the recumbent position a point in the fourth right intercostal space, half the distance from the sternum to the back, was used as the reference point.[3] A cardiac catheter was passed into the right atrium and the recumbent atrial pressure was determined. The patients were then tilted vertically to 90° and were unsupported. In this position the site of the catheter tip was determined fluoroscopically and a point on the anterior surface of the right chest exactly overlying the tip was considered as the reference point. Mean pressures in millimeters of saline were determined in both recumbent and upright positions with the catheter connected to a saline manometer. All patients were allowed to be in the vertical position (standing motionless) until the atrial pressure stabilized; this varied from a minimum of 6 minutes to a maximum of 20 minutes.

RESULTS

There were 13 subjects, 9 normal and 4 with clinical evidence of heart disease, who had recumbent right atrial pressures of 115 mm. of saline or less, averaging 83 mm. of saline. On assuming the upright position, the average reduction of

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this pressure was 88 mm. of saline. Three patients with heart disease had recumbent right atrial pressures ranging from 115 to 160 mm. of saline. In this group the average orthostatic decrease in pressure was 102 mm. of saline. Eleven patients with advanced heart failure, who had recumbent pressures of over 200 mm. of saline, had an average pressure drop of 161 mm. of saline after tilt. Patient T. C., with cor pulmonale, was the only one in this last group whose pressure dropped less than 130 mm. of saline after tilting; he had a pressure fall of only 60 mm. of saline. When his recumbent atrial pressure returned to normal after treatment, he showed a pressure drop of 85 mm. of saline after tilt. The subject with postural hypotension, whose recumbent pressure was 64 mm. of saline, had a total fall of 130 mm. of saline after tilting. Subjects with edema but without clinical evidence of heart failure had normal recumbent right atrial pressures, and when upright, exhibited pressure falls similar to those in normal patients. The results are summarized in Tables I and II. There was no correlation between the time the patients were upright and the total pressure fall that ensued. The average time required for stabilization after tilt in those with recumbent atrial pressures below 115 mm. of saline was 12.3 minutes, while that in those with pressures above 200 mm. of saline was 13.5 minutes.

DISCUSSION

The authors recognize the difficulty in obtaining for the same individual two different reference points that are satisfactory for the determination and comparison of right atrial pressures in the recumbent and vertical positions. No satisfactory alternative method exists short of an intracardiac manometer, the clinical use of which is extremely limited at present. Despite the inherent errors in the method used, it would appear from this study that the higher the right atrial pressure during recumbency, the greater the pressure fall following vertical tilting. When the recumbent pressures and the pressure drops following tilt are compared, the correlation coefficient is 0.77 (Fig. 1). Furthermore, when treatment of heart failure was successful in returning high recumbent atrial pressures to the normal range, the reductions in these pressures following tilting were then of the same magnitude as in normal patients (Fig. 2).

It would appear that in congestive heart failure the venous system can be still further distended in the lower part of the body when the venous pressure in that region is increased on the assumption of the erect posture. The resultant blood trapping, with displacement of blood away from the heart, would lower the intracardiac pressure by reducing intracardiac blood volume. A fairly linear relationship also seems to exist between the level of venous pressure and the rate of fluid filtration from the vascular compartment.[4] One would expect increased movement of fluid out into the tissues when the venous pressure in the lower half of the body increased following tilting. This too would reduce the blood volume, some of which would be intracardiac, and cause a lowering of the right atrial pressure. The role this factor plays in the results obtained in this study is uncertain at present.

If one venous pressure-volume diagram[5] is used, it can be observed that at higher pressures, such as in the range of those in patients in advanced failure,

removal of a given amount of fluid from the vascular system will cause a greater pressure change than removal of the same amount of fluid at lower pressure levels. This diagram was obtained from the inferior vena cava of the dog, and its application directly to man may be open to some question. Gauer[6] found a linear

TABLE I

PATIENT	AGE	SEX	DIAGNOSIS	RIGHT ATRIAL PRESSURE RECUMBENT (MM. OF SALINE)	RIGHT ATRIAL PRESSURE UPRIGHT (MM. OF SALINE)	TOTAL NUMERICAL FALL (MM. OF SALINE)
1. F. H.	50	F	Normal	80	0	80
2. R. F.	32	M	Normal	78	−32	110
3. H. B.	59	M	Normal	114	34	80
4. G. C.	46	M	Normal	85	−15	100
5. R. M.	25	M	Congenital syphilis	70	−70	140
6. E. R.	63	M	Rheumatic aortic stenosis and insufficiency	106	3	103
7. E. M.	54	M	Tetralogy of Fallot	90	15	75
8. S. K.	64	M	Chronic nephritis	100	0	100
9. W. J.	42	M	Hypertensive cardiovascular disease	155	55	100
10. I. H.	42	F	Myxedema heart disease	65	0	65
11. J. A.	35	M	Heart disease, etiology undetermined	106	16	90
12. J. C.	59	M	Chronic nephritis with edema	80	5	75
13. R. H.	26	M	Diabetes; postural hypotension	64	−66	130
14. W. C.	55	M	Lymphosarcoma anasarca	43	−10	53
15. M. B.	50	M	Rheumatic mitral stenosis and insufficiency	160	95	65
16. S. S.	75	M	Coronary artery disease	140	34	106
17. J. S.	21	F	Hypertensive cardiovascular disease	204	64	140
18. M. N.	55	F	Hypertensive cardiovascular disease	210	80	130
19. C. S.	49	M	Hypertensive cardiovascular disease	287	105	182
20. W. R.	65	M	Hypertensive cardiovascular disease	255	110	145
21. T. C.	72	M	Cor pulmonale	290	230	60
Observations repeated after 7 days of therapy				105	20	85
22. R. J.	70	M	Syphilitic aortic insufficiency	290	106	184
Observations repeated after 7 days of therapy				60	−20	80
23. E. D.	43	F	Constrictive pericarditis	238	92	146
Observations repeated 3 months postpericardectomy				117	5	112
24. R. G.	46	F	Rheumatic mitral stenosis and insufficiency	354	170	184
Observations repeated after 14 days of therapy				240	40	200
25. D. W.	30	F	Hypertensive cardiovascular disease	294	105	189
Observations repeated after 14 days of therapy				110	16	94
26. H. W.	44	M	Rheumatic mitral stenosis and insufficiency	326	126	200
Observations repeated after 7 days of therapy				52	−17	69
27. D. J.	64	M	Rheumatic aortic stenosis	240	70	170

TABLE II. SEPARATION OF THE RECUMBENT RIGHT ATRIAL PRESSURES INTO THREE GROUPS, WITH THE AVERAGE PRESSURE FALL OF EACH GROUP FOLLOWING TILTING

	A RECUMBENT R.A. PRESSURE LESS THAN 115 MM.—18 PTS.	B RECUMBENT R.A. PRESSURE OF 115 TO 160 MM. H_2O—3 PTS.	C RECUMBENT R.A. PRESSURE ABOVE 200 MM. H_2O—12 PTS.
Average fall in R.A. pressure when upright	88 mm. H_2O S.D. ± 21.1	102 mm. H_2O S.D. ± 3.4	160 mm. H_2O S.D. ± 39.2

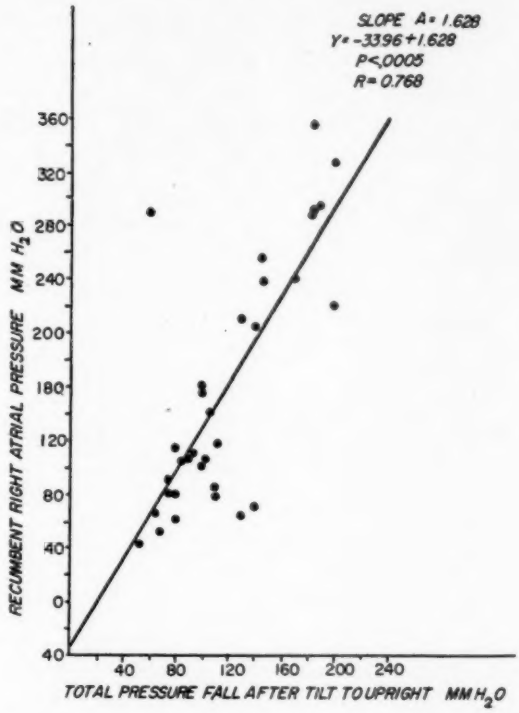
SLOPE A = 1.628
Y = -33.96 + 1.628
P < .0005
R = 0.768
RECUMBENT RIGHT ATRIAL PRESSURE MM H2O
TOTAL PRESSURE FALL AFTER TILT TO UPRIGHT MM H2O

Fig. 1.—The recumbent right atrial pressures are represented on the ordinate, and the reductions in these pressures after tilting are represented on the abscissa. Each point represents a single observation.

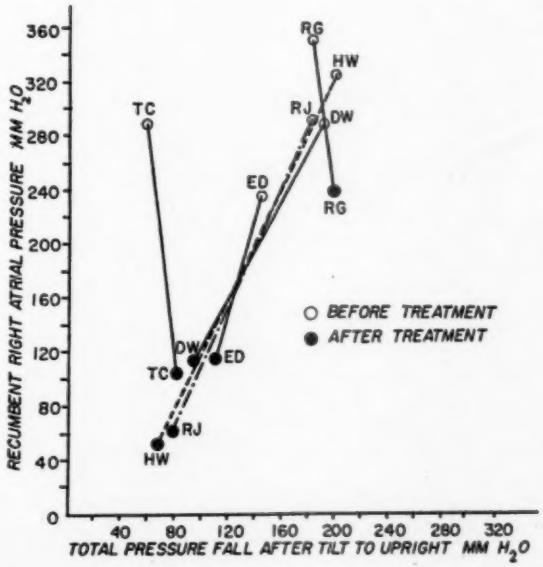

Fig. 2.—The recumbent right atrial pressures are represented on the ordinate, and the reductions in these pressures following tilt are represented on the abscissa. The open circles represent observations before treatment and the closed circles observations on the same patients after treatment for congestive heart failure.

venous pressure-volume relationship of 7 cm. of saline pressure change per 1,000 c.c. of volume change. These studies were done on patients with normal venous pressures.

Another factor to be considered is that displacement of blood away from the heart after tilting increases the cardiac outputs of those patients with congestive failure and thus reduces the atrial pressures. It should be pointed out that right atrial pressure has been clearly reduced in cardiac failure following phlebotomy, without a significant change in cardiac output.[10]

Several observers have pointed out that the pressures in the pulmonary veins and those of the right atrium and great veins change in a similar manner; but these observations were made either on normal individuals or on patients with heart disease without congestive failure.[7,8,9] Apparently, in most instances, the same occurs in congestive failure.[10,11] Therefore, one would expect that, for the most part, a decrease in the central venous pressure would be accompanied by a decrease in the pulmonary venous pressure. Elevated pulmonary venous pressure may be a respiratory stimulus.[12] Likewise, an increase in pulmonary vascular pressures stiffens the lungs, reducing their compliance,[13] and thus increasing the work of breathing. It would seem, therefore, that an orthostatic reduction in these pressures might well be related to orthopnea in heart failure. Also, the relief of paroxysmal nocturnal dyspnea by upright postures might be partially explained on the same basis.

Since the right atrial pressure has been shown to be less in the upright than in the recumbent position, the clinical estimation of the recumbent central venous pressure by noting the level where the neck veins collapse when the subject is semirecumbent would appear to be inaccurate. For the same reason it seems that even though corrections are made for the difference in body position, one cannot use a common reference point and compare recumbent and semirecumbent peripheral venous pressures taken to reflect central venous pressure. These studies indicate that when measuring central venous pressure, one must take the body position into account, and probably also, serial recordings should be made in the same body position to be certain the pressure has stabilized.

The functional residual capacity of the lungs is greater in the upright than in the recumbent position, and is accompanied by a further lowering of the negative intrathoracic pressure.[14] This additional reduction of the pressure in the thorax undoubtedly accounts for a portion of the atrial pressure change observed after tilt, the exact proportion being uncertain at the present time.

Winsor and Burch[15] noted that patients with congestive failure in Classes III or IV had venous pressures 76 mm. of saline lower in the sitting than in the supine position. It should be pointed out, however, that they measured the pressures in an arm vein and the subjects were in a sitting position rather than standing motionless.

SUMMARY

Right atrial pressures, supine and upright, have been measured in 27 patients, 11 of whom had congestive heart failure. Repeat observations were made in 6 of the latter, following treatment of their heart failure. There appears to be

direct correlation between the height of the recumbent right atrial pressure and the total fall of this pressure when the patient is tilted to the vertical position. The factors thought to be responsible for these findings and also the possible relationship of these observations to orthopnea are discussed.

The statistical analyses in this study were performed by the Statistics Laboratory, Department of Mathematics, Ohio State University.

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Aortic Dissection in Pregnancy: A Case of Marfan's Syndrome

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The description of aortic dissection dates back to Morgagni (1682-1771), but not until recently has further development in the understanding of the etiology and pathogenesis taken place.[1-4] Aortic dissection is most frequently seen in patients with malignant hypertension or with coarctation of the aorta. Whether aortic valvular disease and myxedema[5] may predispose for aortic dissection is as yet undetermined.

Recently, reports pointing out the association with pregnancy have appeared in the literature. Schnitker and Bayer,[2] reviewing 49 cases of aortic dissection in young women, found 24 associated with pregnancy. The typical lesion of "idiopathic cystic medial necrosis" may be seen in these instances, but the relationship of pregnancy to the etiology of this condition is not clear at the present time.

Marfan's syndrome is a hereditary disorder of connective tissue, with a high incidence of cardiovascular malformations,[6] and aortic dissection is a frequent complication, although not described until 1943, by Etter and Glover.[7] Lathyrism has been produced experimentally in growing rats by a diet of sweet-pea meal (*Lathyrus odoratus*). Incidentally, multiple lesions such as scoliosis, hernias, and aortic dissection were noted, and ascribed to a failure of the ground substance. Bean and Ponseti[8] pointed out the many similarities between Marfan's syndrome and this experimental disorder, and suggested that a related but not necessarily identical dysfunction caused both conditions.

The present report was prompted by our observation of a patient with Marfan's syndrome in whom aortic dissection occurred in the early part of pregnancy.

CASE REPORT

L. M., a Jewish woman first seen in 1947, at the age of 22 years, complained of shortness of breath and palpitation. A harsh systolic murmur with a sharp second sound was heard over the

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base of the heart, and numerous extrasystoles were noted. The blood pressure was normal. This same year a curettement had been done following an early spontaneous abortion. An ECG, in 1948, revealed normal sinus rhythm with ventricular premature contractions, left axis deviation, and nonspecific T-wave changes.

In October, 1949, she was delivered of a full-term male infant after 10-hour labor, and in February, 1951, she was again delivered of a full-term male infant after 6-hour labor.

A chest roentgenogram in 1953, revealed a heart of left ventricular configuration which was slightly enlarged (Fig. 1,*A*). An ECG remained unchanged, as did auscultatory findings. She was advised not to become pregnant.

On Oct. 30, 1955, the patient was hospitalized because of excruciating substernal pain extending through to the mid-back and radiating into both temporal areas and right arm. The pain had begun as vague substernal discomfort 2 days previously, and had improved temporarily, only to become suddenly worse with accompanying weakness and air hunger on the day of admission.

The patient was 30 years old at this time, and was found to be 22 weeks pregnant. The cardiac apex was in the sixth intercostal space and anterior axillary line. A loud systolic murmur of to-and-fro character was heard over the base of the heart, radiating to the neck vessels, and a sharp second aortic sound was noted. The blood pressure was unobtainable on the right arm. On the left it was 90/40 mm. Hg. Arterial pulsations were absent on the right arm, markedly reduced in both carotids, and present in the left arm and both legs. Periorbital ecchymosis was noted on the right. A tentative diagnosis was made of aortic dissection, and conservative treatment instituted.

A roentgenogram of the chest on admission (Fig. 1,*B*) showed further cardiac enlargement and mild congestive changes in the lungs, and an ECG revealed tachycardia and additional "ischemic changes." Admission hemoglobin was 11.3 Gm.; it rose subsequently to 12.7 Gm. White blood cell count went from 15,650 per cubic millimeter on admission to 21,800, and finally dropped to 9,000. Erythrocyte sedimentation rate reached 102 mm. per hour (Westergren) 11 days after admission.

The pain gradually decreased in intensity, and 5 days after onset of dissection, pulsations were again noted in the right radial and ulnar arteries.

It became apparent shortly after admission that the patient had Marfan's syndrome. She was 167 cm. tall, with wider span than length, and demonstrated dorsal kyphosis, winged scapulae, genu valgum, and pes planus. The extremities were thin, the fingers and toes "spider-like" in shape (see roentgenogram, Fig. 1*E*), and she wore an 11 AAA shoe. The muscular tonus was poor and diastasis recti was present. Most joints in the extremities could be hyperextended at will by the examiner. Marked cysto- and rectocele were present, as were varicosities of the legs. No abnormalities of the eyes were noted.

The patient's 3 children have not been examined, but one son has pectus excavatum, another very thin, long fingers and toes.

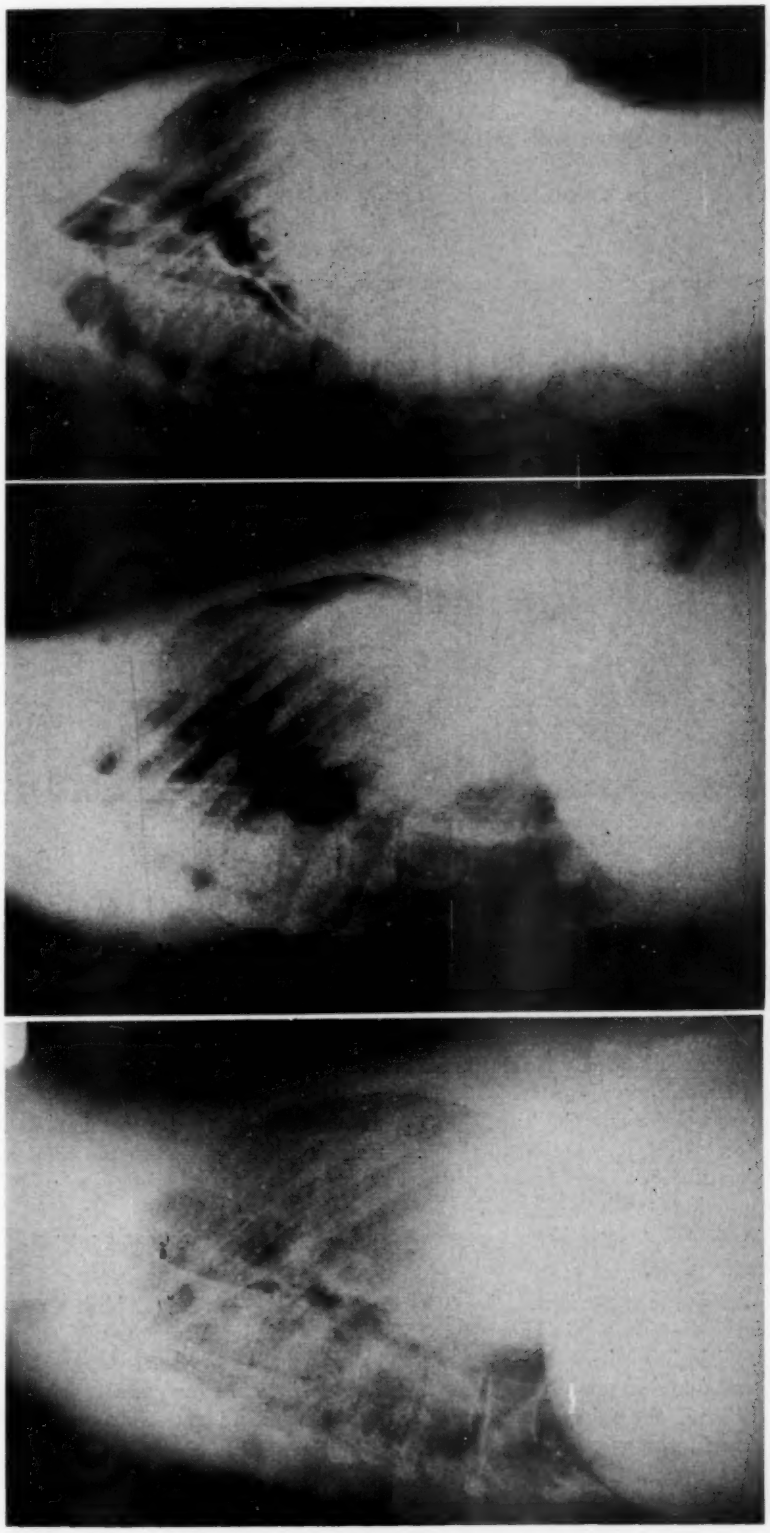
During the course of her illness the patient sustained several episodes with bigeminal pulse, supraventricular tachycardia, congestive failure, etc. She also experienced several bouts which were considered repeated dissections. Three weeks after the initial dissection the patient complained of severe pain in the chest, right side of the neck, and right arm; and the right radial, ulnar, and carotid pulses again disappeared for a couple of days. Two weeks later the patient complained of pain in the left carotid sheath, and a tender pulsating structure was observed in the area. The improvement was slow and the patient was discharged to her home.

One month later, in January, 1956, the patient experienced another spell of severe chest pain, with soreness and swelling of both carotid arteries and decreased pulsations in both arms lasting for 1 week, and another dissection was suspected.

Consultation was held as to method of delivery and it was decided to deviate from the usual management of functional Class III multiparous cardiacs. Cesarean section was chosen instead of delivery from below for two main reasons. First, the anticipated strain was presumed to be less, with less chance of extension of dissection or rupture of the aorta. Secondly, all factors relating to therapy could be controlled and maintained at an optimum at the scheduled time.

A. *B.* *C.* *D.*

Fig. 1.—Roentgenograms of the chest in aortic dissection in a case of Marfan's syndrome. *A*, April 18, 1953: Left ventricular configuration of the heart with slight enlargement. *B*, Oct. 30, 1955: Right after start of aortic dissection, further cardiac enlargement. Note aortic shadow on lateral projection. *C*, Feb. 21, 1956: After several episodes considered as repeated dissections, further cardiac enlargement. Note further widening of aortic shadow on posteroanterior and lateral projections. *D*, Oct. 5, 1956: Further cardiac enlargement to right and left. Further widening of aortic shadow.



D.

C.

B.

Fig. 1.—*(For legend see opposite page.)*

The patient was hospitalized 2½ weeks before the expected date of confinement (March 7, 1956). The heart had increased further in size, and the roentgenographic shadow of the ascending and first part of the descending aorta was widened (Fig. 1, *C*).

After 1 week of hospitalization low segment section was performed by one of us (L. L. F.) and a normal male infant weighing 3,300 grams was extracted and cried spontaneously. Bilateral tubal ligation and excision of the mid-portion of each tube was then performed. Nitrous oxide, oxygen, 2 ounces of 0.5 per cent Novocain and 250 mg. of intravenous Pentothal were used for anesthesia.

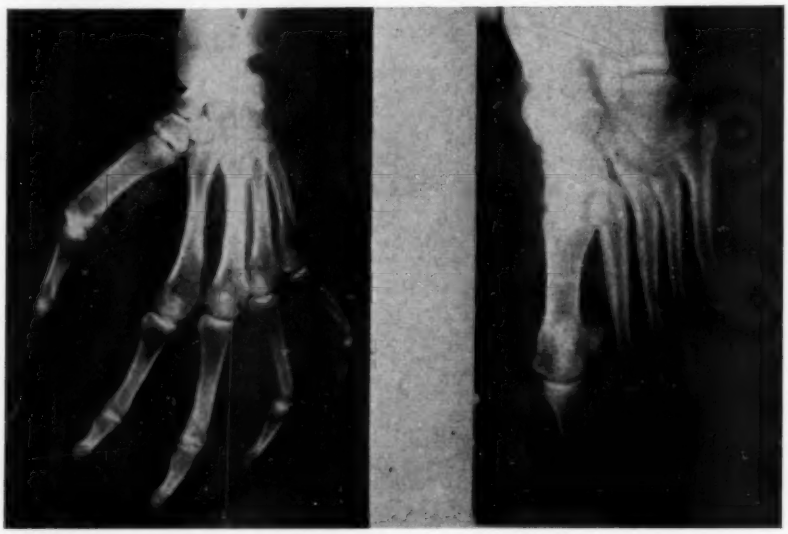


Fig. 1*E*.—Roentgenogram of left hand and foot.

The postoperative course was essentially uneventful and mother and baby were discharged 2½ weeks after the section on restricted activity.

Further cardiac enlargement gradually took place and the condition deteriorated. A Grade 3 systolic murmur and a loud tambour aortic second sound appeared over the base of the heart, and a Grade 1 systolic murmur was present over the apex. A blowing diastolic murmur was noted along the left sternal border. A relative insufficiency of the tricuspid valve appeared, with marked liver enlargement and pulsations. The legs were edematous but the lungs relatively clear to auscultation; there were no complaints of chest pain. A roentgenogram of the chest in October, 1956, 8 months after delivery, revealed further enlargement of the heart to the right and left, and further widening of the descending aorta (Fig. 1,*D*). An ECG at this time showed no significant change from previous tracings (Fig. 2).

The patient expired suddenly on Dec. 7, 1956—about 13 months after the initial dissection of the aorta had taken place.

Necropsy.—Necropsy was performed by Charles W. Jarvis, M. D.* The body measured 167 cm. and weighed an estimated 60 kilograms. The heart (see Fig. 3) was totally enlarged and weighed 720 grams with the entire aorta attached. The myocardium measured up to 17 mm. over the left ventricle, and up to 10 mm. over the right. The aortic valve measured 11 cm. in circumference, the mitral 14 cm., the pulmonary 10 cm., and the tricuspid 15 cm. An anatomically open but functionally closed foramen ovale was noted.

Approximately 2.5 cm. above the aortic ring a transverse tear (Fig. 3, *2*) was found in the aortic wall, involving the intima and part of the media. The tear extended around the aortic

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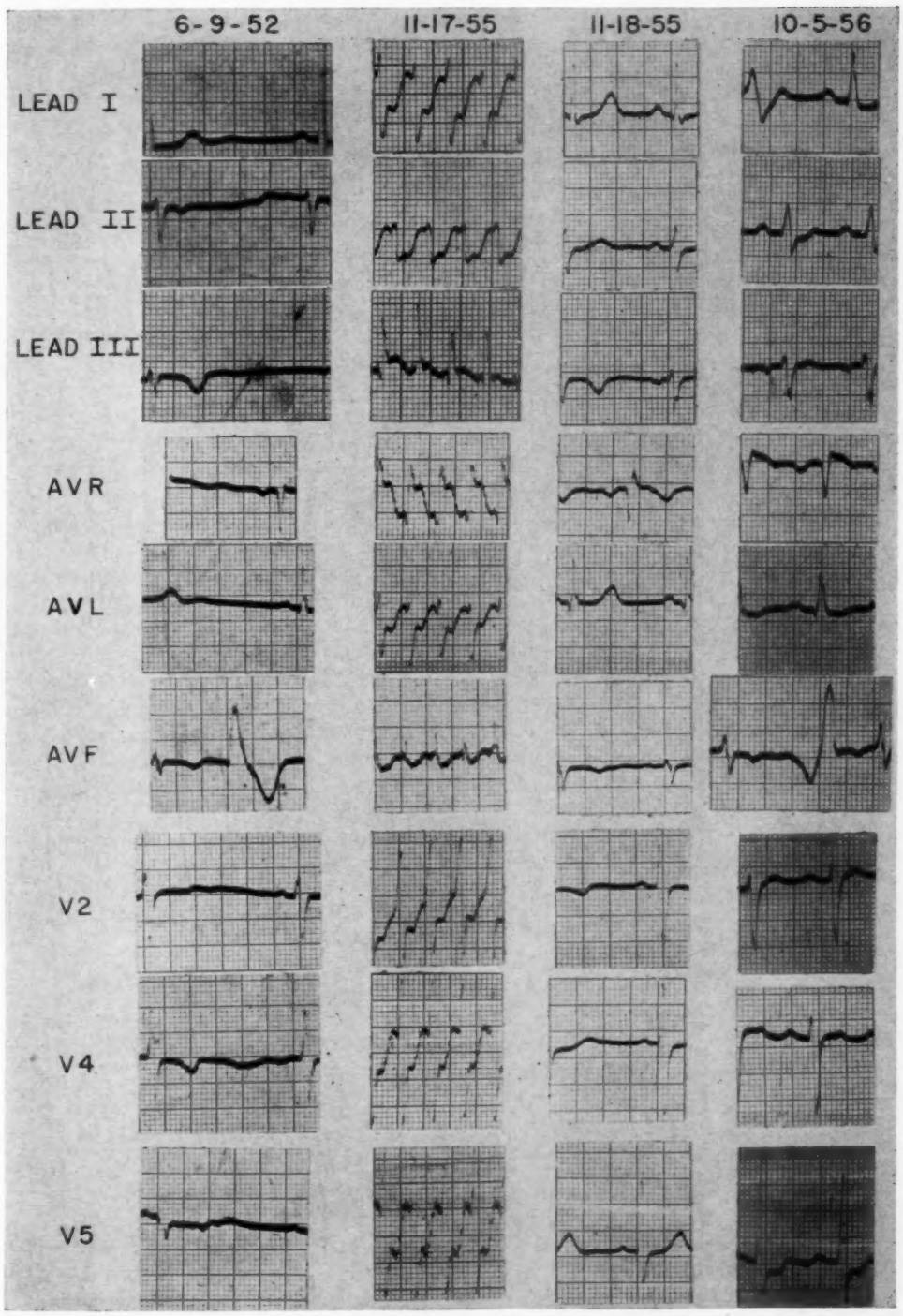

Fig. 2.—Electrocardiographic tracings from patient with aortic dissection and Marfan's syndrome. 6-9-52: Nonspecific T-wave changes—stationary findings before aortic dissection. 11-17-55: Ventricular tachycardia. 11-18-55: Reversion of same. 10-5-56: Same as before—but with additional strain and digitalis effect.

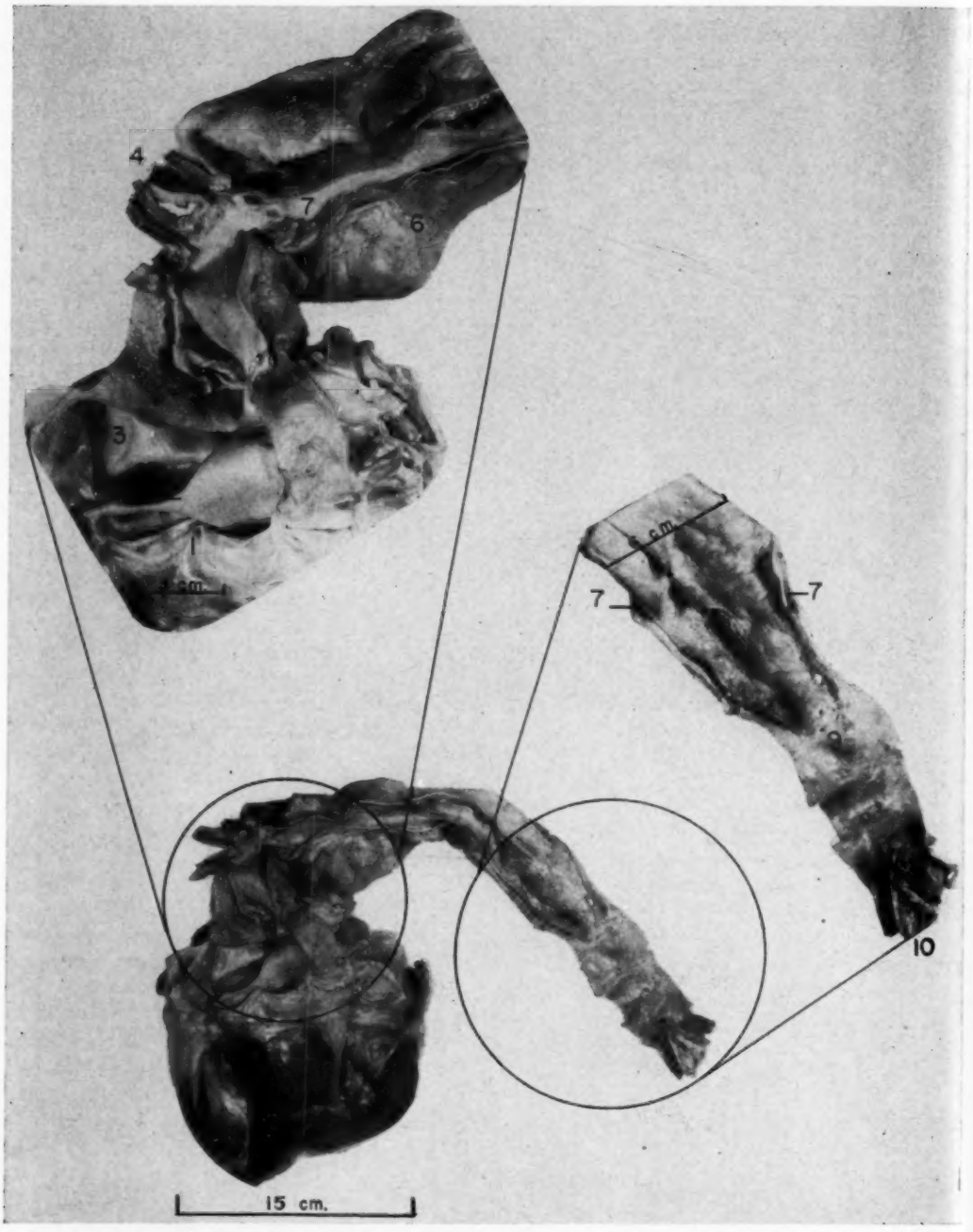

Fig. 3.—Aortic dissection in a pregnant woman with Marfan's syndrome. *1*, Aortic cusps. *2*, Primary tear in the aortic intima and media, leading into *3*, the primary extraluminary channel formed by the first occurring dissection. *4*, Arteries to neck and arms showing extension of the dissection. *5*, Subsequent tear in the wall of the primary dissection leading into *6*, the second extraluminar channel. *7*, True lumen of the aorta. *8*, Re-entry of the second extraluminar channel into the primary extraluminar channel. *9*, Re-entry of the primary dissection into the abdominal aorta. *10*, Bifurcation of the aorta.

circumference, except for a small area posteriorly. The root of the aorta—made up of the rest of the media and the adventitia—was dilated and measured 17 cm. in circumference. Beginning 5 cm. above the aortic cusps a diffuse narrowing of the true aortic lumen (*7*) was noted, varying in circumference from 6 to 3 cm. The abdominal aorta (*9*) measured 1.8 cm. in circumference. The root of the aorta communicated with a dissection (*3*) around the true lumen of the aorta (*7*) which re-entered the true aorta in the abdominal portion (*9*). A secondary dissection started with a tear (*5*) in the wall of the first dissection just distal to the origin of the left subclavian artery and extended downward (*6*) around the two previous channels to a point (*8*) just proximal to the origin of the renal arteries, where it re-entered the first dissection. The first dissection extended into the innominate artery and its branches and into the left carotid and subclavian arteries (*4*). All channels contained blood. The wall of the abdominal aorta distal to the re-entry (*9*) of the dissection appeared to be quite thin.

Death was ascribed to congestive failure, and chronic passive congestion was observed in the lungs, liver, spleen, and gastrointestinal tract.

Microscopic Findings.—(See Fig. 4.) Study of the aortic wall revealed only minor atheromatous changes.

A section from the thoracic aorta (Fig. 4, *1*) revealed gross preservation of the elastic structures around the true aortic lumen (*A*—entering into the cut from the left upper corner). However, the elastic tissue seemed decreased in amount. The outer layer of the media with its elastic components could be traced into the outer layer (*B*) of the wall of the channel (caused by the aortic dissection and facing left lower corner of the cut), whereas the inner layer of this latter wall (*D*) was greatly thickened and sclerosed with absence of elastic as well as muscle tissue. Endothelial lining was noted in both channels.

A higher magnification from the wall of the thoracic aorta (Fig. 4, *2*) revealed not only decrease in the amount of elastic tissue, but also focal disruption of the elastic laminae. The remnants of the elastic tissue formed clumps and irregular clusters and the smooth muscle tissue seemed secondarily disorganized. No accumulation of chromotrophic substance nor cyst formation was noted.

A cross section of the abdominal aorta distal to the area of dissection (Fig. 4,*3*) showed the wall to be quite thin, as a result of an absolute decrease in elastic tissue. Minor focal disruption of elastic laminae was present (Fig. 4, *3*—middle third), causing some retraction and clumping of the smooth muscle cells with minor disturbance of their circumferential arrangement. Higher magnification (Fig. 4, *4*—lower third) of the same area revealed only minor disturbance of the architecture of the elastic tissue.

A section from the skin revealed no significant changes.

DISCUSSION

Many excellent reviews of the different aspects of aortic dissection have appeared in the literature[1-4,9] and repetition seems unwarranted.

At least three different factors may have contributed to the dissection in our case, namely, hypoplasia of the aorta, Marfan's syndrome, and pregnancy. Hypothetical toxic or metabolic factors (myxedema, diet, etc.) and hypertension were absent. Coarctation of the aorta also carries a high risk of aortic rupture, and about 10 per cent of patients with coarctation will experience a rupture with or without dissection. The significance of the diffuse hypoplasia of the aorta as a mechanical factor in the dissection in our case is open for discussion.

Degenerative changes are observed to a variable degree in the media at the base of the aorta in instances of aortic dissection ("idiopathic cystic medial necrosis" of Erdheim), and disappear gradually toward the origin of the innominate artery. Actually two histologically distinct varieties are described,[3] depending upon whether the smooth muscle or the elastic tissue element is primarily

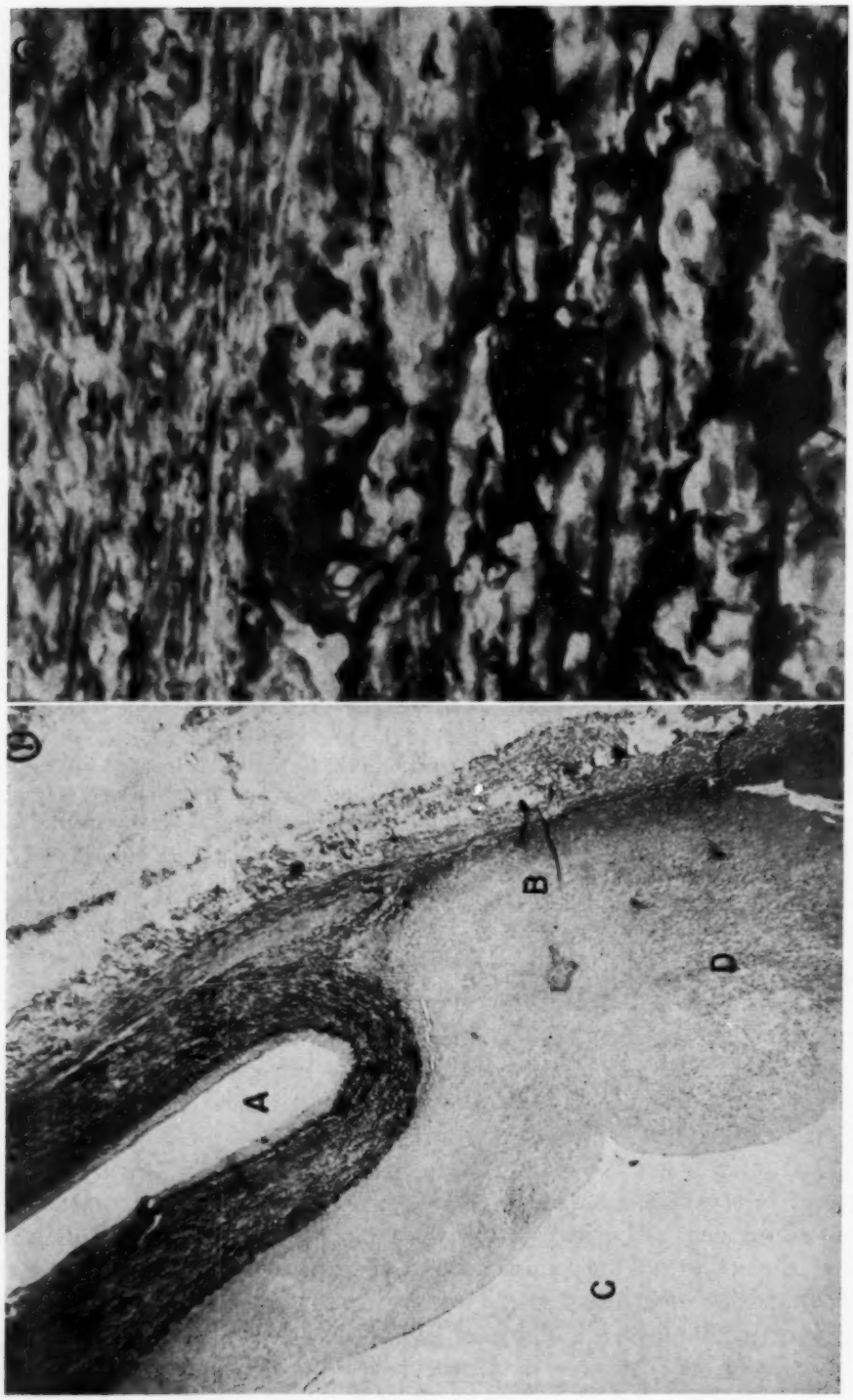

Fig. 4.—*(For legend see opposite page.)*

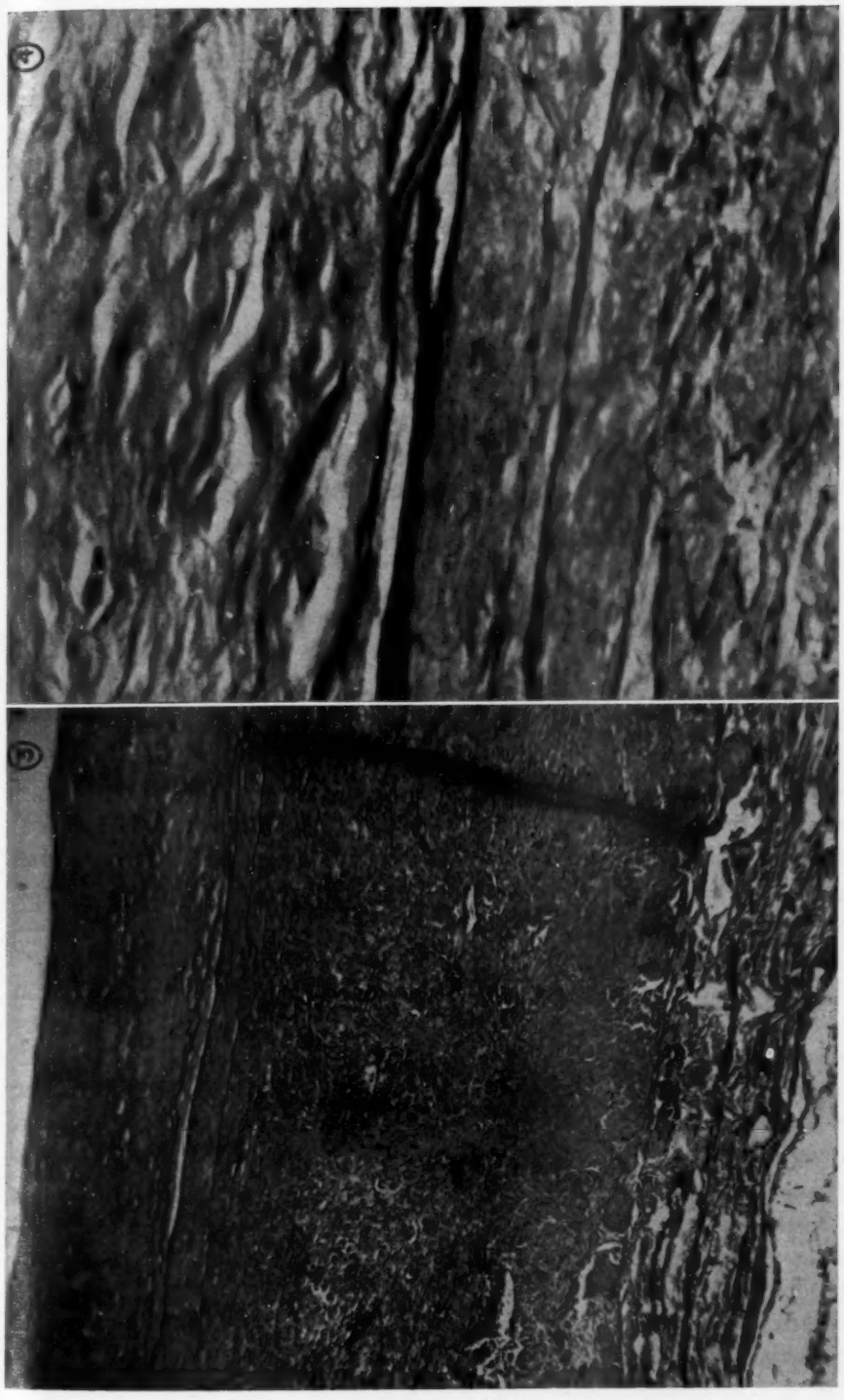

Fig. 4.—Aortic wall (elastic van Gieson's stain). *1*, Section from thoracic aorta (×14; reduced 1/7). True aortic lumen (*A*) enters from left upper corner—wall of the channel formed by dissection (*C*) facing left lower corner. Thinning of elastic tissue in the aortic wall. Outer layer of the media with elastic components (*B*) continues into the wall of the false channel (*C*). Thickening and sclerosis of the endothelialized wall (*D*) of the channel. *2*, Section from the media of the thoracic aorta (×450; reduced 1/7). Elastic laminae broken up with formation of irregular clusters of elastic material. Disorientation of smooth muscle tissue. *3*, Cross section from the abdominal aorta (×70; reduced 1/7). Absolute decrease in elastic tissue with diminution of the wall thickness. Minor disruption of the elastic laminae with only mildly disordered smooth muscle structures. *4*, Same as *3* (×450; reduced 1/7).

involved. The muscle degeneration variety, usually seen in the group over 50 years of age, is characterized by vacuolization and focal loss of smooth muscle cells, whereby secondarily an attenuation and condensation of the elastic fibers take place, with loss of the normal wavy pattern. In the elastic tissue variety, seen in the group under 40 years of age, there is a focal disruption of the elastic laminae, with secondary disarrangement and retraction of the smooth muscle fibers. Each type exhibits features of the other, and the intermediate age group have a combination type of disorder. In either type basophilic mucinous material may appear and form cystlike structures spreading the normal tissue remnants apart. Thin-walled, widely patent vessels penetrate the defective medial, so that the wall becomes thicker than before, but also more vulnerable.

The start of aortic dissection in the large majority of cases is due to a rupture in the weakened media caused by the combined effects of mechanical forces involved, and by the differences in elasticity between the different layers of the aorta. The vasa vasorum are torn and a "hematoma" formed, which may increase in size and cause a cleavage with rapid proximal and distal dissection. The newly formed channel may re-enter the aorta or penetrate further into the surrounding tissue.

In severe atherosclerosis of the aorta numerous minimal ruptures originating in atherosclerotic plaques may be observed without evidence of further dissection. Shennan[1] reported that only 2.5 per cent of his series of aortic dissection were caused in this manner.

McKusick's description[6] of the aortic changes in Marfan's syndrome corresponds to an elastic type of media degeneration. Inasmuch as Marfan's syndrome is an abiotrophy, McKusick maintains that the proximal aorta will "wear out" prematurely from the maximal arterial pressure (and pulse waves), and sooner than the distal portion. The histologic changes, accordingly, should become most marked in the ascending aorta. A relaxation of the aortic ring with secondary aortic insufficiency may occur and aortic dissection, either alone or coexisting with a diffuse aneurysm, may take place. A similar elastic tissue degeneration was noted in the areas of dissection in our case.

In addition, less elastic tissue was present throughout the entire aorta than normally encountered. Thus, in the abdominal aorta, and distal to the dissection, the elastic tissue was markedly diminished in amount (Fig. 4, *3*), and no invasion by blood vessels observed. Our findings raise the question as to whether Marfan's syndrome is only a disorder of the elastic *fiber*, or is also characterized by a *general decrease in elastic tissue bulk*.

Recently, aortic dissection and other changes, such as hernias and kyphosis, ascribable to defects in the ground substance have been produced experimentally in growing rats by a sweet-pea diet. Death from aortic dissection occurred in from 38 to 75 per cent of the animals. Ponseti and co-workers[8] observed loss of cohesion with patchy necrosis of the smooth muscle cells in the aortic media of the animals, whereas the elastic fibers remained unchanged. Next, the intima ruptured at the site of medial weakening, and dissection took place. Bean and Ponseti[3] reviewed 20 human necropsy cases of aortic dissection, and found kyphoscoliosis or pigeon-breast deformity in 35 per cent, which is higher than chance

occurrence. They suggested that many instances of "cystic media necrosis" were caused by a disorder of ground substance which also could cause bone matrix failure and ventral hernias. The basic fault could be genetic, dietary or metabolic in nature, and Marfan's syndrome was suggested as a related dysfunction, genetically transmitted. Because of the apparent histologic and pathogenetic differences between the experimentally induced aortic dissection and the dissection in Marfan's syndrome, a direct relationship seems unlikely to the present authors.

McKusick investigated 50 families where Marfan's syndrome occurred, and found 105 affected persons. The genetic data suggested a single mutant gene as responsible for all aspects of this multifaceted disease.

McKusick suggested that the elastic fibers were at fault, causing such anomalies of the eye as ectopia lentis, myopia, retinal detachment, and abnormal configuration of the cornea. In the cardiovascular system, changes causing diffuse aneurysms and dissections were noted in the media of the aorta and pulmonary arteries. Patent foramen ovale, mild hypoplasia of the aorta, and redundant chordae tendineae with valvular regurgitation were frequently noted—coarctation of the aorta and persistent ductus more rarely. In the skeletal system notable anomalies included dolichostenomelia and -cephaly, highly arched palate, pigeon-breast, pectus excavatum, kyphoscoliosis, muscular hypotonia, hyperextensibility, and subluxation of the joints, deafness, hernias, etc.

Our case shows many of the features of Marfan's syndrome, although none were found in the ocular system. According to McKusick, 20 per cent or more of patients with Marfan's syndrome have no eye complications.

A habitus with long, thin extremities suggestive of Marfan's syndrome is not rare in the general population. Most of these are merely anthropologic variants. However, aortic dissection associated with this habitus certainly strongly suggests Marfan's syndrome as the basic disorder. The possibility of formes frustes of the complete syndrome in ascending and descending line should be kept in mind. Mutation, according to McKusick, accounts for only 15 per cent of all instances of Marfan's syndrome.

Reports of aortic dissection in connection with pregnancy have appeared periodically in the literature since 1832 (Elliotson[10]). "Cystic medial necrosis" has been described under these circumstances, but also as an accidental finding in pregnancy without aortic dissection.[2]

A general loosening of connective tissue has been observed in lower animals toward term. If we may be allowed conjecture, a relationship between pregnancy and loosening of connective tissue, aortic degeneration and dissection may be postulated in the female.

To review the features pertaining to aortic dissection in pregnancy the authors searched the literature and found a total of 51 cases,[2,11-13] including the present one (see Tables I and II). Of the 43 patients with stated age, an equal number occurred in the third and fourth decades. Only 3 patients were over 40 years of age.

In 6 instances coarctation of the aorta was noted as an additional finding.[12,14-18] A certain degree of hypoplasia of the aorta was observed repeatedly,

but the protocols were not accurate enough to permit an estimate of incidence and severity of this anomaly, and the incidence of pre-existing hypertension could not be determined. A number of the reported cases were not observed prior to the dissection, and many patients were reported normotensive before the onset of the aortic dissection, as was our patient.

Only two other instances of aortic dissection in pregnancy (those of Lindeboom and co-worker[19] and Carpent and associates[20]) were diagnosed as Marfan's syndrome. McKusick[6] did not observe ill effects from pregnancy in his series of Marfan's syndrome. Three instances of Marfan's syndrome in 51 cases of aortic dissection is, however, a higher incidence than chance permits. Possibly the incidence of Marfan's syndrome as the cause of aortic dissection in pregnancy may be underdiagnosed, because of its rarity and the dramatic presenting picture of the dissection itself.

In 18 of the 51 cases the number of pregnancies was not stated. Sixteen were gravida I, 4 were gravida II, 7 were gravida III, and in 6 the dissection occurred in the fourth or later pregnancy. The patients of Lindeboom and co-worker[19] and Carpent and associates[20] were both pregnant for the first time. Our patient was gravida IV.

In all but one case information was available as to the time of dissection. Three patients experienced dissection in the first trimester, 12 in the second, and 35 in the last trimester. Only 17 patients went to term. Four instances of

TABLE I. AORTIC DISSECTION ASSOCIATED WITH PREGNANCY: 51 CASES

MOTHER'S AGE	CASES	MULTIPARITY	CASES	GESTATION AGE AT THE TIME OF AORTIC DISSECTION	CASES
20–29	19	Gravida I	16	First trimester	3
30–39	21	Gravida II	4	Second trimester	12
Over 40	3	Gravida III	7	Third trimester	35 (17 of same at term*)
		Gravida IV or more	6		

*Dissection took place post partum in 7 instances, and started during labor in 4 instances.

TABLE II. FETAL SURVIVAL IN 51 CASES OF AORTIC DISSECTION ASSOCIATED WITH PREGNANCY*

	LIVING BABIES
7 post-mortem cesarean sections	5
7 instances of onset of aortic dissection post partum	5
1 cesarean section after onset of aortic dissection with labor	1
2 instances of aortic dissection in second trimester delivered by cesarean sections toward term	2

*Complete information was not always available in the literature, and the true number of living babies may be higher than our figures indicate.

dissection have been observed with the onset of labor pains, and an additional 7 in the puerperium. This time relationship strongly suggests that certain metabolic changes conducive to elastic tissue degeneration take place in pregnancy.

CONCLUSIONS

"Cystic medial necrosis" is a histopathologic picture caused by several different factors rather than by one etiologic and morphologic entity. It represents the last link in a chain of events starting out with either elastic tissue degeneration of the aorta (as observed in Marfan's syndrome, aortic dissection of the young normotensive individuals, pregnancy), smooth muscle tissue degeneration (as seen in aortic dissection of older normotensive individuals), ground substance failure (induced by sweet-pea diet in rats), or possibly sclerosis in small medial vessels in malignant hypertension. Following the initial step, further degeneration takes place until the full-blown picture of cystic medial necrosis with aortic dilatation or dissection is apparent.

A combination of two or more factors, or addition of, for instance, hypertension, increased stroke volume, or coarctation of the aorta, may further enhance the degenerative processes. Both a disruption of the elastic fibers as observed in the areas of aortic dissection of our case, and a decrease in elastic tissue mass as noted in the abdominal aorta distal to the dissection, may be characteristic histologic features in Marfan's syndrome.

SUMMARY

1. A review of the literature on aortic dissection is presented, emphasizing the different etiologic and pathogenetic factors involved and their specific histologic features. Aortic dissection in the young individual is characterized by an early degeneration of the elastic tissue components of the aortic medial layer, as is aortic dissection in pregnancy and Marfan's syndrome. Following the degeneration of the elastic laminae, secondary changes are observed in the smooth muscle tissue, with ingrowth of numerous thin-walled vessels and development of cystic mucin-filled spaces, whereby the aortic wall becomes markedly weakened and susceptible to dissection.

2. A case of Marfan's syndrome with aortic dissection during pregnancy is presented exhibiting less elastic tissue bulk in the aorta than normally seen. The question is raised as to whether an absolute decrease in elastic tissue mass is a constant feature in Marfan's syndrome in addition to the fragmentation of the elastic laminae previously described.

3. Repeated bouts of aortic dissection were observed from the twenty-second throughout the thirty-first week of pregnancy in the present case of Marfan's syndrome, finally leading to the development of a triple-barreled aorta. Cesarean section was done electively 2 weeks before term, with delivery of a normal male infant. After delivery no further episodes of dissection were recognized. The patient expired in congestive failure 13 months after onset of dissection, which was 8 months post partum.

4. We believe that gestation enhanced the aortic dissection and shortened

the patient's life. It is prudent to individualize termination of pregnancy in each case, depending on the stage of gestation at which the dissection occurs. Interruption of the early pregnancy is recommended as soon as the cardiac condition is stabilized. If possible, whenever the gestation is in the third trimester, the patient should be carried to viability of the fetus and delivery by cesarean section.

The authors feel that one should deviate from the usual management of obstetric care in aortic dissection and that cesarean section is the method of choice for termination of the pregnancy after viability of the fetus is assured.

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Observations on Conduction in a Case of Intermittent Left Bundle Branch Block

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Most reports of cases of intermittent left bundle branch block indicate that there is a critical rate above which the bundle fails to conduct and below which normal conduction occurs.

Recently we have had the opportunity to make detailed observation of the relation of conduction to cycle length during repeated transitions from normal conduction to left bundle branch block, and vice versa. The transitions were induced by (1) the change in cycle length resulting from carotid sinus stimulation, and (2) the change in cycle length attending sinus arrhythmia associated with taking a deep breath.

Each cycle length of the record showing the transitions was measured and was plotted on coordinate paper, employing a circle if the following QRS complex showed the presence of block, and a dot if conduction was normal (Fig. 1).

The observation that we wish to report may be examined in Fig. 2. Here it is noted that as the heart slowed, bundle branch block persisted until the cycle length exceeded a duration of 0.94 second. On the other hand, in the same sequence, as the heart accelerated, normal conduction, once established, persisted until the cycle length fell below 0.88 second. This phenomenon was observed many times. Ashman[1] noted a similar phenomenon in a study of QRS aberrations that occur in auricular fibrillation. In connection with the latter phenomenon he offered an explanation that is adapted to the present case in the diagram of Fig. 3. *A*, *B*, and *C* are contiguous regions of the diseased left bundle branch. *B* is so greatly depressed that it constitutes a gap in the bundle insofar as conduction is concerned. *A* and *C* are portions of the bundle branch that are simply depressed. Investigations of conduction in nerve fibers in which such a gap has been produced by cocainization indicate that a blocked impulse produces potential changes in that portion of the nerve (*C*) below the block (*B*), lowering its threshold to excitation (Wedensky,[2] Blair,[3] Lorente Di No[4]). Presumably the excitatory effect of the electrotonic flow produced by the depolarization of the

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portion *A* just proximal to the block (Fig. 3) upon the portion of the fiber distal to the block (*C*) may be sufficiently great to cause excitation of the latter. The impulse may jump the gap by a sort of "saltatary conduction." Whether this occurs depends upon the excitability of *C* at the moment that *A* is depolarized. The excitability of *C* at any moment must depend upon the duration of time that it has had for recovery from previous excitation, more than upon any other factor.

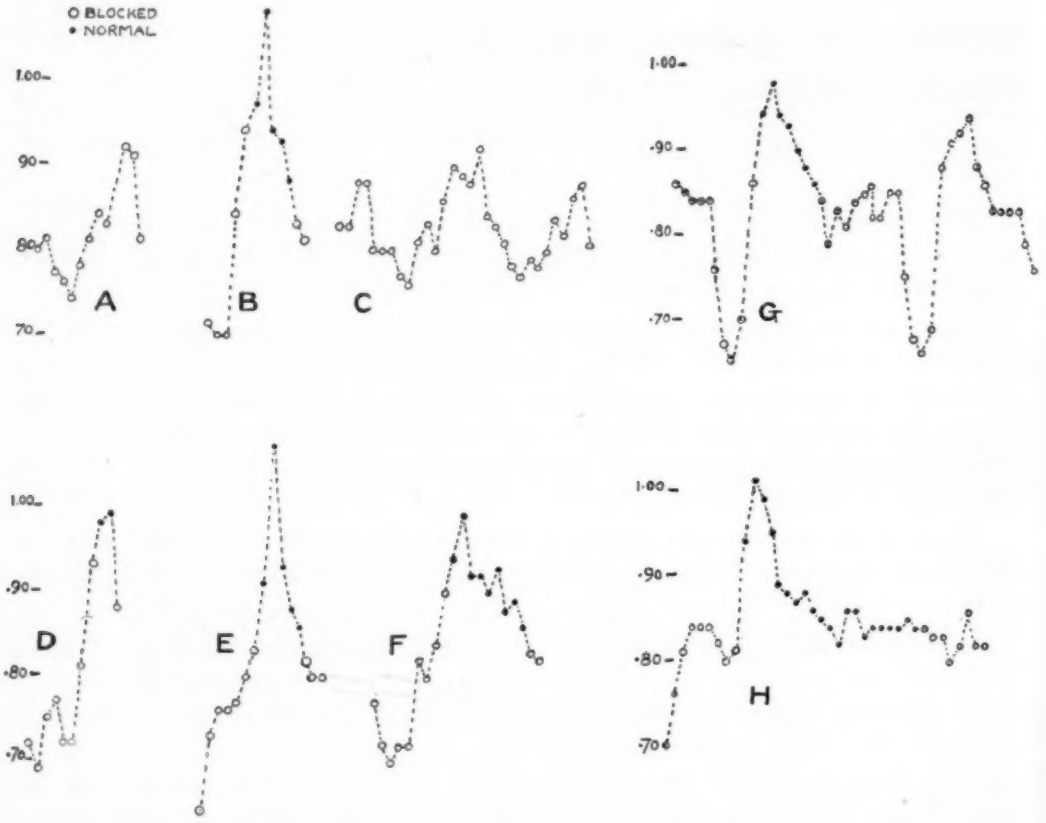

Fig. 1.—Eight sequences of beats showing the relation between cycle length and conduction in the left bundle branch, observed in the case presented. The beats showing left bundle branch block are represented by circles; those in which conduction was normal are represented by dots. Note that left bundle branch block did not disappear until cycle length was increased to more than 0.94 second, but that once normal conduction was established it persisted until the cycle length fell to 0.88 second.

Excitation across the gap cannot occur unless the excitability at *C* has reached a certain critical level at the moment that the impulse reaches the blocked region, *B*. Obviously, if the impulse is blocked at *B*, and *C* is not depolarized, the latter region will have the time furnished by the succeeding cycle length to complete its recovery. Thus, after the cycle length following the blocked beat, the impulse should jump the gap and 2:1 left bundle branch block should occur. It does not. As a matter of fact, 2:1 left bundle branch block is a relatively rare phenomenon.

The phenomenon observed in this case and also the rarity of 2:1 left bundle branch block may possibly be explained as follows: When conduction is blocked at *B*, *C* is depolarized by the impulse conducted by the right bundle branch after it traverses the thickness of the interventricular septum (Fig. 4). If the time required for the traversal of the septum is assumed to be 0.10 second, the sequence of events may be diagrammed as in Fig. 4. If *C* requires a recovery time of 0.90 second in order to make it possible for excitation to jump the gap (*B*), then conduction, once established, will ordinarily be successful as long as the cycle length

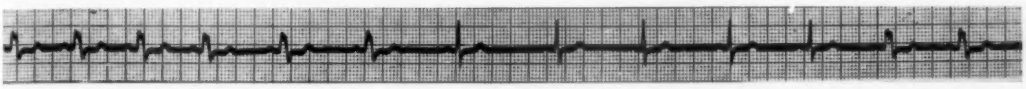

Fig. 2.—Lead V_6 of the record from which the sequence of Fig. 1, *B* was plotted.

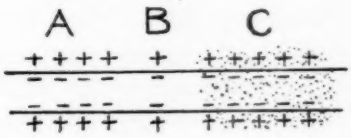

Fig. 3.—A diagrammatic representation of the diseased left bundle branch. *A* is the normal conducting fiber; *B* is the segment which is poorly polarized so that it is unresponsive and therefore constitutes a "gap" in the fiber; *C* is the segment of depressed fiber distal to the gap.

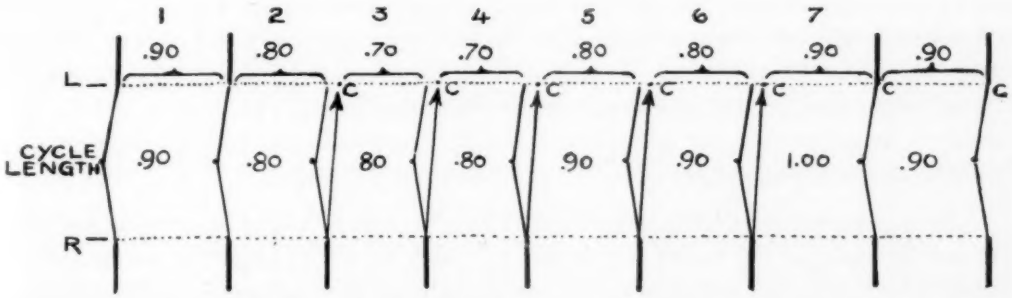

Fig. 4.—Diagrammatic representation of the explanation offered for the behavior of conduction in the case under discussion. The heavy vertical lines *L* and *R* represent conduction in the corresponding bundle branch. The arrows represent conduction of the impulse from the right bundle branch through the septum to the segment *C* of the left bundle branch (see Fig. 3). The time figures over the brackets are the intervals afforded for recovery of the segment *C* of the left bundle branch. See text for explanation.

remains at or above 0.90 second. If the cycle length falls to 0.80 second (*2*, Fig. 4), *C* cannot be excited across gap *B*, and block occurs. However, the excitation is conducted through the right bundle branch to and through the interventricular septum and arrives at *C*, as has been assumed, 0.10 second after the excitation of *A*; and *C* is depolarized. If another cycle of 0.80 second duration occurs (*3*, Fig. 4), *C* has now only 0.70 second for recovery when the impulse reaches *A*; again, excitation cannot jump the gap, and block occurs once more.

When the impulse after traversing the right bundle branch and intraventricular septum reaches *C*, the latter has had 0.80 second for recovery, and while this recovery period is not sufficient to permit excitation of *C* across the gap, it is ample for the greater excitation by the greater effect of the excitatory process which is conducted directly to it through the septum without an intervening block. Wedensky facilitation may play a part. Thus, *C* is again depolarized. If the cycle length now increases to 0.90 second (*5*, Fig. 4), the impulse arrives at the gap *B* when *C* has had only 0.80 second for recovery, and, as has just been explained, block again occurs. We now have block at a cycle length that had previously permitted conduction (*1*, Fig. 4). Furthermore, since *C* requires a recovery time of 0.90 second to permit its excitation across the gap, the cycle length must now reach 1.00 second to permit successful conduction (*7*, Fig. 4). Following a cycle length of 1.00 second the cycle length may fall again to 0.90 second, and normal conduction persists. Note in Fig. 4 that the recovery period for *C* is the same for a cycle length of 1.00 second as it is for a cycle length of 0.90 second.

It is apparent that later, during the period of observation, the critical time required for recovery of *C* diminishes, for as heart rate increases, block does not occur until the cycle length diminishes to 0.78 second, whereas earlier, block occurs nearer 0.84 second. Correspondingly, when the heart slowed in the later observations, conduction was resumed at cycle lengths as short as 0.88 second. Possibly with a lower average rate some recovery from "accumulated fatigue" occurs. It is also possible that the occurrence of block without change of cycle length noted in sequence H (Fig. 1) may be due to "accumulated fatigue" when the cycle length is near the critical level. A previous report by Bohnengel[5] of the same phenomenon was accompanied by other explanations, involving changes in the physiologic condition of the conducting tissues attributed to congestive heart failure and alterations in coronary circulation.

SUMMARY AND CONCLUSIONS

In a case of intermittent left bundle branch block it was observed that during acceleration of the heart, a significantly shorter cycle length was required to induce block than was required to re-establish normal conduction when the heart was slowing.

A theoretical explanation of this phenomenon is offered.

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The Mean Manifest Electrical Axis of the Ventricular Activation Process (ÂQRS) in Congenital Heart Disease: A New Approach in Electrocardiographic Diagnosis

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The determination of the mean manifest electrical axis of the ventricular activation process (ÂQRS) in cases of congenital malformation of the heart has been proved very useful in clinical practice. A left axis deviation in a cyanotic case strongly suggests tricuspid atresia, and the diagnosis of Fallot's tetralogy becomes improbable. In the presence of right bundle branch block with ÂQRS deviated to the left, total or partial persistent common atrioventricular canal can be suspected. These examples show the importance of determining the location of ÂQRS in congenital heart disease.

As far as we know, the position of ÂQRS in congenital heart disease has been studied in only two papers.[70,96] The ÂQRS position in each of the main malformations of the heart was studied in the first paper[70]; the investigators proceeded from the disease to the electrical axis. In the present article we first study the ÂQRS position, and through it the different diagnostic possibilities are suggested; we also analyze all the possible axis deviations for each of the main congenital entities, in the same manner as in the paper mentioned above.[70]

We have noted to our surprise that in most cases the main clinical diagnosis is obtained by a careful analysis of the tracing. At the end of this paper we present some examples of the procedure employed in the interpretation.

MATERIAL AND METHOD

A series of 1,331 electrocardiograms corresponding to congenital heart cases were studied, focusing special attention on the ÂQRS position (Table I). Most of the tracings studied were reviewed from medical literature,[1-96] and some of them were from the files of the Instituto Nacional de Cardiología. All the selected cases were diagnosed by means of clinical and laboratory (catheterization) methods and proved during surgery or by autopsy (see Table I).

ÂQRS was determined by measuring positive and/or negative areas enclosed within the deflections. Bayley's triaxial system was used to plot and study axial distribution.

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TABLE I

CONGENITAL CARDIAC MALFORMATIONS ACCORDING TO INCIDENCE OBSERVED IN OUR SERIES	NUMBER OF CASES	PERCENTAGE
Fallot's tetralogy	284	21.34
Patent ductus arteriosus	207	15.55
Interatrial septal defect	162	12.17
Coarctation of the aorta	136	10.21
Fallot's trilogy	108	8.11
Pure pulmonary stenosis	99	7.44
Tricuspid atresia	93	6.98
Interventricular septal defect	79	5.94
Ebstein's disease	51	3.83
Persistent common atrioventricular canal	31	2.33
Congenital aortic stenosis	23	1.73
Single ventricle	16	1.20
Eisenmenger's complex	16	1.20
Transposition of the great vessels	14	1.06
Common trunk	9	0.68
Fallot's pentalogy	3	0.23
Total number of cases	1,331	

RESULTS

Fig. 1 shows the distribution by frequency of the main cyanotic congenital heart diseases in each of the sextants of the triaxial system. Fig. 2 shows similar distribution for the acyanotic group. These figures help to establish the differential diagnosis of congenital heart disease from the viewpoint of electrocardiography. This is only one aspect of a complete and thorough electrocardiographic interpretation.

For a more comprehensive analysis of Figs. 1 and 2, each sextant will be studied separately.

CONGENITAL CARDIAC MALFORMATIONS WITH CYANOSIS

A. *Cases Located in Sextant VI of Bayley (0° to +59°). Normal ÂQRS Position (Fig. 1).*—The 3 main malformations whose axes are present in this sextant are: tricuspid atresia, Ebstein's disease, and single ventricle. We can discard the following entities: Fallot's tetralogy and pentalogy, transposition of the great vessels, and persistent common atrioventricular canal.

Since the differential diagnosis between tricuspid atresia and single ventricle is sometimes difficult to establish, the following are valuable electrocardiographic signs:

1. *Usual findings in tricuspid atresia (Fig. 3):* (a) Broad, deeply notched, tall and peaked P waves are recorded in the standard leads. Usually the P waves in Leads I and II show two peaks and the height of the first peak is greater than that of the second. Diphasic P waves appear in V_1 and V_2. (b) Signs of left ventricular enlargement are observed: incomplete left bundle branch block, delayed intrinsicoid deflection in the left precordial leads, small R waves from V_1 through V_4 with high R waves in V_5 and V_6, secondary RS-T segment and T-wave changes, etc.

2. *Usual findings in single ventricle (Fig. 4):* (a) P waves are normal or show slight changes in the standard leads. (b) Complexes of the rS or RS type appear in all the precordial leads.

We know very little about the tracing of single ventricle because of the small number of cases we have observed, and because no information is available regarding the sequence of the activation process in this malformation.

3. *Frequent electrocardiographic findings in Ebstein's disease (Fig. 5):* (a) Right bundle branch block is a frequent finding. The unipolar precordial morphology corresponding to the left ventricle in the presence of right bundle branch block (complexes of the qRS type with a broad and slurred S wave and positive T wave) is recorded in several precordial leads (V_3 through V_6, for example). (b) The unipolar precordial morphology of the right atrium in the presence of right bundle branch block (qR complexes with slurring of the R wave and negative T waves) may be found in several right precordial leads (V_1 through V_3 or V_4, for example). This pattern suggests important right atrial enlargement. (c) If no right bundle branch block is present, or if it is present in minor degree, QR type complexes with negative T waves (auricular potential variations) may be registered in several right precordial leads. We have seen tracings with these complexes in all the precordial leads. This morphology corresponds to a huge right atrial dilatation.

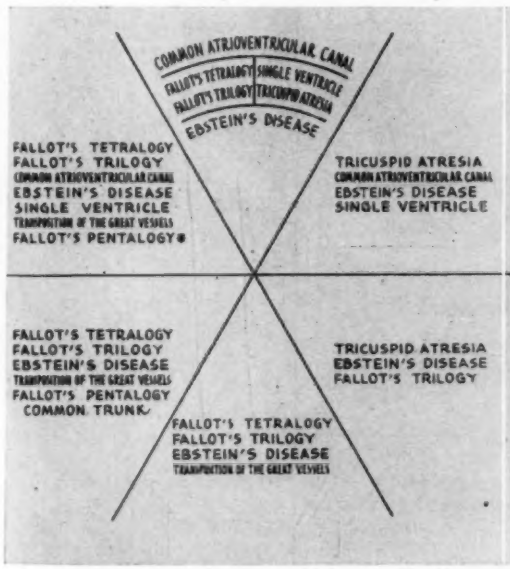

Fig. 1.

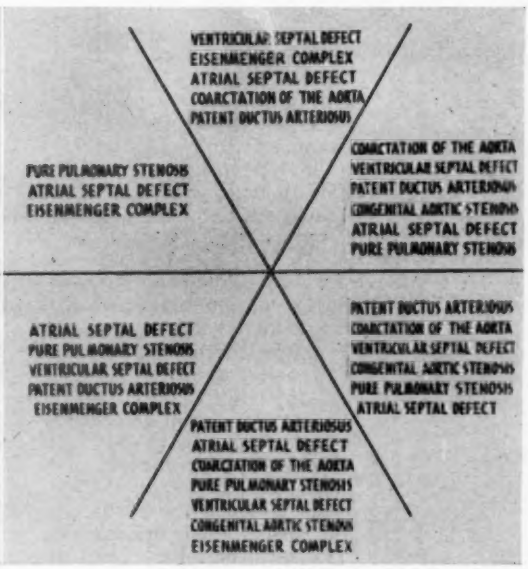

Fig. 2.

Fig. 1.—Distribution of cyanotic congenital cardiac malformations (according to frequency). Those malformations under 0.9 per cent incidence are not included.

***Cases not included in the original series.**

Fig. 2.—Distribution of acyanotic congenital cardiac malformations (according to frequency). Those malformations under 0.9 per cent incidence are not included.

(d) In the presence of sinus rhythm the P-wave changes may be contributory signs: tall and peaked P waves with a slight slurring in both limbs. These changes suggest important right atrial enlargement. Peaked and tall P waves may be registered in several precordial leads. If, on the other hand, the P waves are broad, concomitant left atrial enlargement is suggested. The right and left atrial dilatation depends upon the atrial septal defect as well as the main congenital anomaly. The highest P waves we have observed are in Ebstein's disease and in tricuspid stenosis of rheumatic origin. (e) Frequent arrhythmias are: auricular fibrillation and flutter, auricular and ventricular premature beats, and paroxysmal auricular tachycardia. (f) The presence in children of Wolff-Parkinson-White syndrome Type B should suggest the possibility of Ebstein's disease. (g) First degree A-V block is a frequent finding.

B. *Cases Located in Sextant I of Bayley* ($-1°$ *to* $-60°$) [*Fig. 1*].—The malformation with the highest incidence here is tricuspid atresia, and the common left axis deviation found in this sextant is explained by the hypertrophy and dilatation of the left ventricle and the counterclockwise rotation of the heart.

TABLE II. ÂQRS POSITION IN CONGENITAL MALFORMATIONS OF THE HEART

LOCATION AND MALFORMATION	PERCENTAGE (FOR EACH ONE OF THE SEXTANTS)
Sextant I of Bayley ($-1°$ to $-60°$)	
Tricuspid atresia	46.0
Coarctation of the aorta	17.9
Ventricular septal defect	9.1
Persistent common atrioventricular canal	7.9
Patent ductus arteriosus	7.2
Ebstein's disease	3.2
Congenital aortic stenosis	2.7
Atrial septal defect	2.6
Single ventricle	1.3
Pure pulmonary stenosis	0.7
Fallot's tetralogy	0.7
Common trunk	0.7
Fallot's pentalogy	0.0
Fallot's trilogy	0.0
Transposition of the great vessels	0.0
Eisenmenger's complex	0.0
Sextent II of Bayley ($-61°$ to $-120°$)	
Persistent common atrioventricular canal	20.0
Single ventricle	16.0
Tricuspid atresia	14.0
Fallot's tetralogy	14.0
Fallot's trilogy	12.0
Ventricular septal defect	10.0
Ebstein's disease	4.0
Eisenmenger's complex	4.0
Atrial septal defect	2.0
Coarctation of the aorta	2.0
Patent ductus arteriosus	2.0
Transposition of the great vessels	0.0
Pure pulmonary stenosis	0.0
Common trunk	0.0
Congenital aortic stenosis	0.0
Fallot's pentalogy	0.0
Sextant III of Bayley ($-121°$ to $\mp 180°$)	
Fallot's tetralogy	61.4
Fallot's trilogy	12.3
Persistent common atrioventricular canal	10.3
Pure pulmonary stenosis	4.0
Ebstein's disease	4.0
Single ventricle	2.0
Atrial septal defect	2.0
Eisenmenger's complex	2.0
Transposition of the great vessels	2.0
Coarctation of the aorta	0.0
Congenital aortic stenosis	0.0
Ventricular septal defect	0.0
Fallot's pentalogy	0.0
Patent ductus arteriosus	0.0
Common trunk	0.0
Tricuspid atresia	0.0

Persistent common atrioventricular canal (Fig. 6) starts to appear in this sextant, but, in general, its electrocardiographic pattern is quite characteristic and the differential diagnosis with tricuspid atresia, Ebstein's disease, and single ventricle (the other main diseases found in this sextant) can be easily established.

TABLE II. ÂQRS POSITION IN CONGENITAL MALFORMATIONS OF THE HEART—(CONT'D)

LOCATION AND MALFORMATION	PERCENTAGE (FOR EACH ONE OF THE SEXTANTS)
Sextant IV of Bayley (+179° to +120°)	
Fallot's tetralogy	44.8
Fallot's trilogy	15.0
Atrial septal defect	12.3
Pure pulmonary stenosis	10.4
Ebstein's disease	5.2
Ventricular septal defect	2.7
Eisenmenger's complex	1.8
Patent ductus arteriosus	1.8
Transposition of the great vessels	1.8
Fallot's pentalogy	1.8
Common trunk	0.9
Single ventricle	0.6
Coarctation of the aorta	0.6
Persistent common atrioventricular canal	0.3
Tricuspid atresia	0.0
Congenital aortic stenosis	0.0
Sextant V of Bayley (+119° to +60°)	
Patent ductus arteriosus	22.6
Atrial septal defect	18.4
Fallot's tetralogy	16.0
Coarctation of the aorta	10.6
Pure pulmonary stenosis	9.6
Fallot's trilogy	7.1
Ventricular septal defect	6.3
Ebstein's disease	2.9
Congenital aortic stenosis	2.1
Transposition of the great vessels	1.1
Eisenmenger's complex	0.9
Common trunk	0.8
Tricuspid atresia	0.5
Persistent common atrioventricular canal	0.5
Single ventricle	0.3
Fallot's pentalogy	0.3
Sextant VI of Bayley (+59° to 0°)	
Patent ductus arteriosus	35.9
Coarctation of the aorta	29.6
Tricuspid atresia	9.4
Ventricular septal defect	8.7
Ebstein's disease	5.0
Congenital aortic stenosis	4.4
Pure pulmonary stenosis	2.1
Atrial septal defect	2.1
Fallot's trilogy	2.1
Single ventricle	0.7
Fallot's tetralogy	0.0
Fallot's pentalogy	0.0
Eisenmenger's complex	0.0
Common trunk	0.0
Transposition of the great vessels	0.0
Persistent common atrioventricular canal	0.0

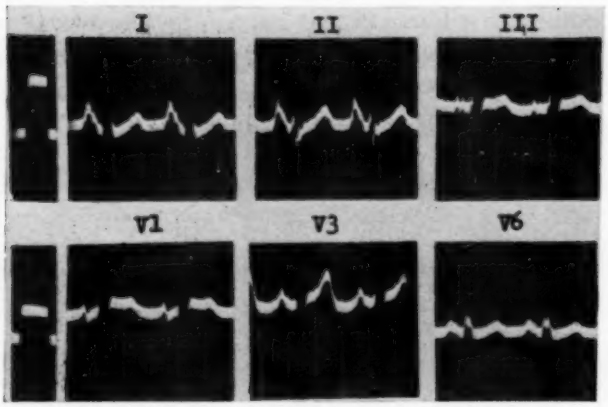

Fig. 3.—Tricuspid atresia. Note the peaked and tall P waves with notchings and slurrings in Leads I and II. ÂQRS is around −40°. There is incomplete left bundle branch block as it is recognized in V_6.

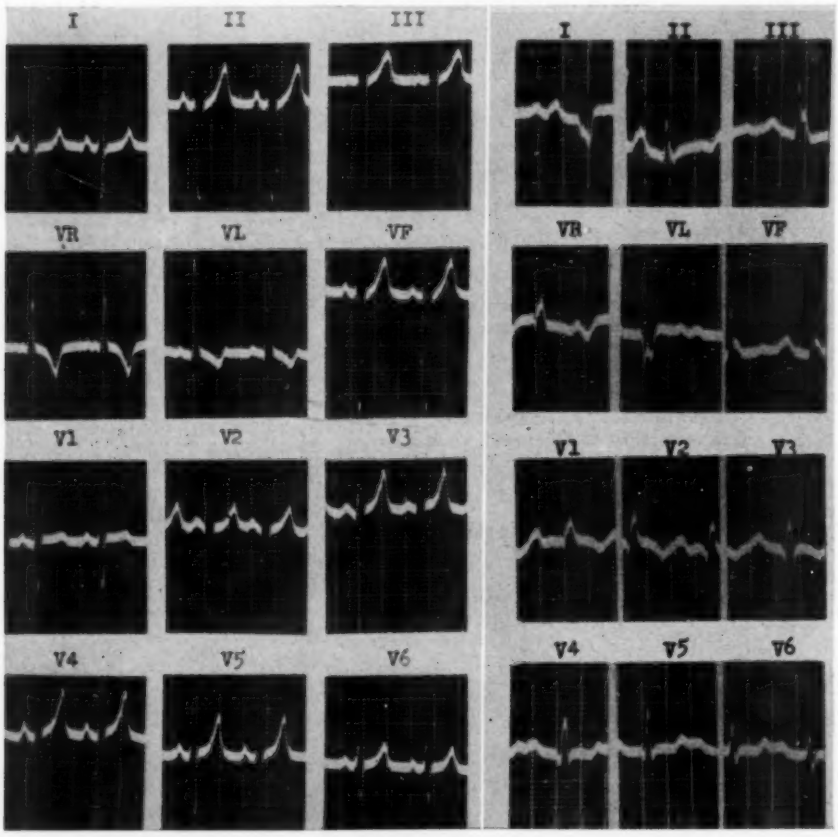

Fig. 4. Fig. 5.

Fig. 4.—Single ventricle. The R waves remain relatively small in all precordial leads, and isodiphasic complexes are registered from V_4 through V_6. The P wave remains normal and ÂQRS is placed around −75°.

Fig. 5.—Ebstein's disease: right bundle branch block is present. Complexes of the qR type are inscribed in V_1 and V_2, and of the qRs type from V_3 through V_5, suggesting marked right atrial dilatation. The high and slurred P waves in Leads I, II, and V_F reinforce this diagnosis.

Frequent electrocardiographic findings in persistent common atrioventricular canal (total or partial type of congenital anomaly): (a) Right bundle branch block with left axis deviation is observed. This type of tracing is also found in ostium primum. The left axis deviation is a consequence of the high R waves in Lead I and deep S waves in Lead III; the strong forces of activation of the free left ventricular wall are paramount during the cardiac cycle. (b) There are signs of right ventricular hypertrophy: the R′ in the right precordial leads has a high voltage. (c) Signs of left ventricular hypertrophy are present. The tall R wave in the left precordial leads and the left axis deviation are very suggestive of strong left ventricular forces. (d) There is important voltage of the main deflections in all leads.

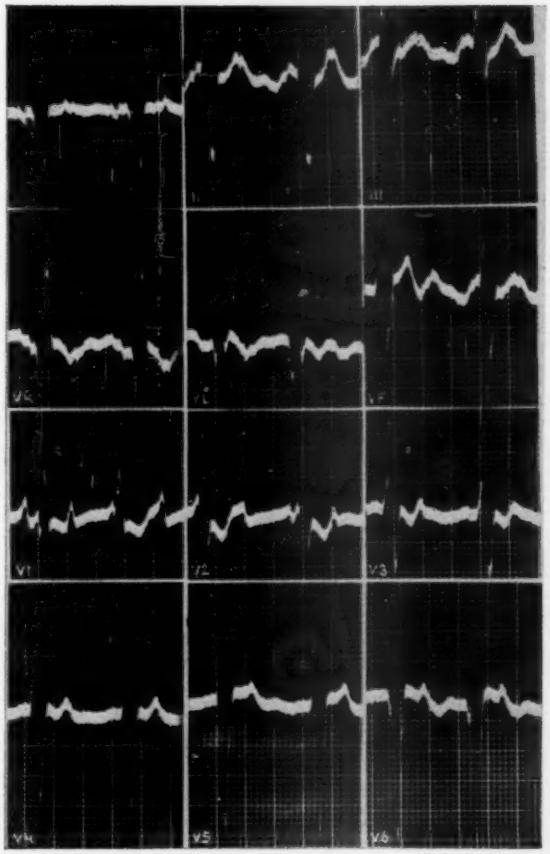

Fig. 6.—Persistent common atrioventricular canal. There is paroxysmal auricular tachycardia with an auricular rate of 200 per minute. Right bundle branch block with ÂQRS around −75°. The R waves are tall in all the precordial leads, suggesting biventricular enlargement.

C. *Cases Located in Sextant II of Bayley (−61° to −120°) [Fig. 1].*—Persistent common atrioventricular canal is the malformation with the greatest incidence, followed by single ventricle, tricuspid atresia, and Fallot's tetralogy and trilogy which have a somewhat similar incidence. It is important to note that while persistent common atrioventricular canal is distributed throughout this sextant, single ventricle and tricuspid atresia are located between −61° and −90° (only one case of each of these entities was located beyond −90°). All but one of the cases of Fallot's trilogy and tetralogy were found between −91° and −120°.

Following are the contributory signs in differential diagnosis of Fallot's trilogy and tetralogy.

1. *Usual findings in Fallot's tetralogy (Fig. 7):* (a) Peaked and tall P waves are found in Leads I and II ("congenital P waves"); sometimes in Leads II and III. Diphasic P waves with predominance of the positive phase and with rapid inscription of the intrinsicoid deflection appear in the same right precordial leads. (b) Right ventricular hypertrophy is present: high R waves with complexes of

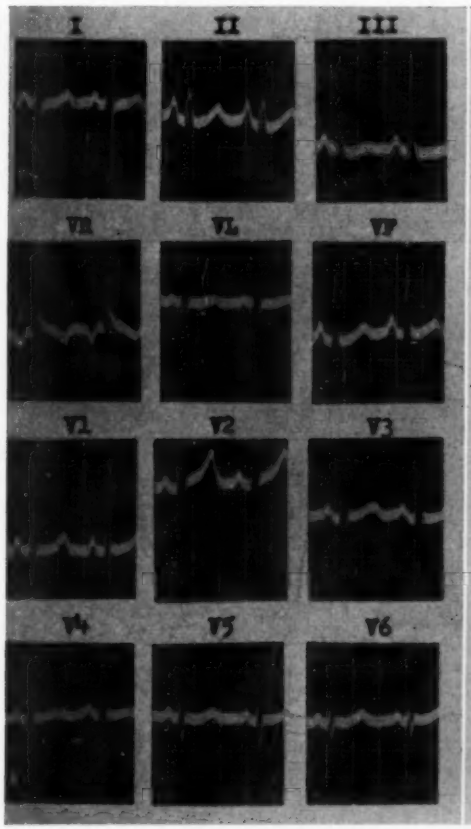

Fig. 7.

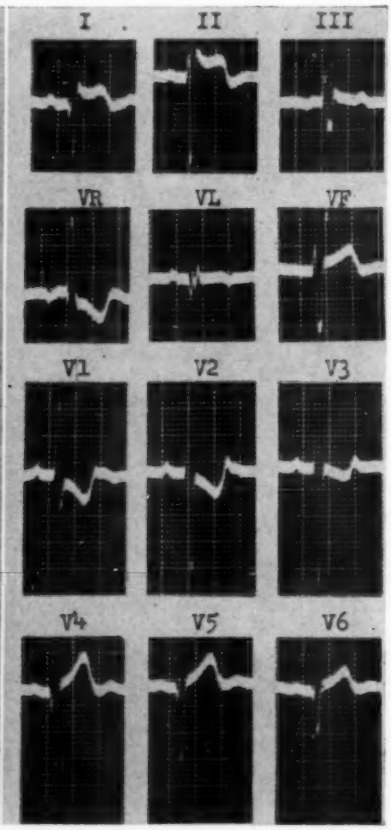

Fig. 8.

Fig. 7.—Fallot's tetralogy. The ventricular complex is of the Rs type in V_1; of the rS from V_2 through V_6. Note the positive T waves in all the precordial leads and the characteristic P-wave changes.

Fig. 8.—Fallot's trilogy. In differentiating this tracing from Fig. 7 it is important to notice the negativity of the T waves from V_1 through V_3, the high R waves in the same leads, and the complexes of the qRS type with positive RS-T displacement in Leads I, II, and V_6.

the R (with initial slurring of the upstroke), Rs or rR type in the right precordial leads. Small R waves with deep S waves are recorded in the left precordial leads. In these cases there is important hypertrophy of the middle and low third of the free right ventricular wall. (c) Complexes of the rS type in the right precordial leads suggest that the precordial electrode is exploring the trabecular zone of the right ventricle. In these cases the ventricular hypertrophy is predominant in the basal regions of the right ventricle around the crista supraventricularis. An abrupt change from complexes with tall R and small S to rS complexes is frequently recorded from V_1 to V_2 or V_2 to V_3. (d) The T wave may be negative in Lead V_1 and exceptionally so in other right precordial leads. In some cases the T wave is positive in all the precordial leads. This characteristic T-wave behavior helps to establish the differential diagnosis with Fallot's trilogy. When the T wave is negative in V_1, it generally becomes positive in V_2 or V_3.

2. *Usual findings in Fallot's trilogy (Fig. 8):* (a) The P waves are similar to those described in Fallot's tetralogy. (b) The same electrocardiographic signs of right ventricular hypertrophy as described above in Fallot's tetralogy are observed. Complexes with tall R waves appear in more right precordial leads in trilogy than in tetralogy. On the other hand, complexes of the rS type in several right precordial leads are exceptional in trilogy. Complexes of the QS, QrS or rS type are frequently recorded in left precordial leads. (c) Negative T waves, sometimes of the ischemic type, are a common finding in several right precordial leads. This helps to establish the differential diagnosis with Fallot's tetralogy. (d) One of us (G.A.M.) recently described the following electrocardiographic findings which are very suggestive of Fallot's trilogy: positive displacement of the RS-T segment with positive T wave more often in Leads I and V_L, and less frequently in Leads V_5 and V_6; if the RS-T displacement is not present, the T waves may be tall and peaked instead.

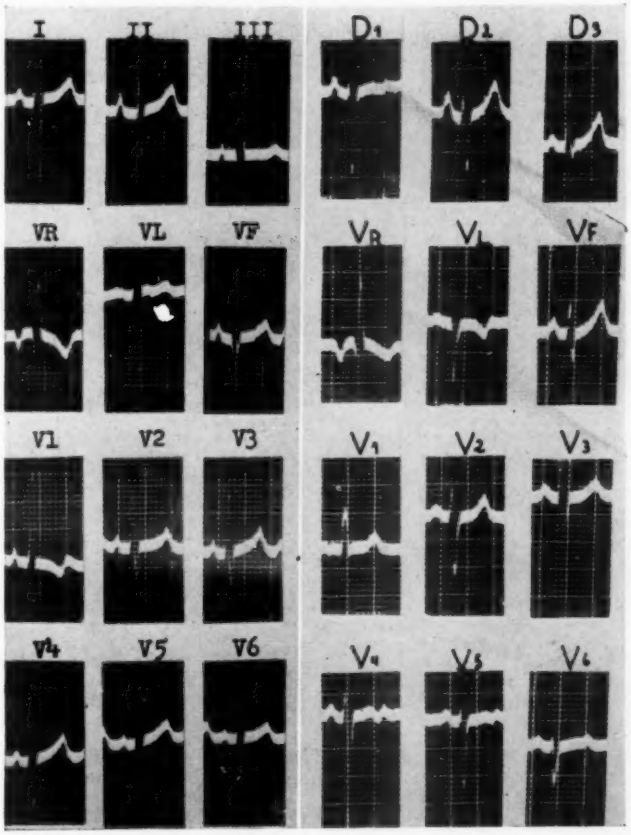

Fig. 9. Fig. 10.

Fig. 9.—Fallot's pentalogy. The diagnostic clue in this tracing is the presence of complexes of the left ventricular type (clean R with slurred and notched S, with positive and peaked T wave) from V_2 through V_6.

Fig. 10.—Transposition of the great vessels. The diagnosis is reached through the T-wave changes: positive and tall T waves in the right precordial leads with small and notched T waves in V_5 and V_6.

D. *Cases Located in Sextant III of Bayley (Between −121° and ∓180°).*—Fallot's tetralogy is the congenital anomaly with the greatest incidence, by far, in this sextant. Therefore, in a patient with early and marked cyanosis in which ÂQRS is located between −121° and ∓180°, the most probable diagnosis is

Fallot's tetralogy. Persistent common atrioventricular canal and Fallot's trilogy show a very low incidence in relation to tetralogy (see Table II).

In this same sextant, but with very low incidence, the following malformations are also present: Ebstein's disease, single ventricle, and transposition of the great vessels. Few cases of Fallot's pentalogy have been observed in these positions recently. The electrocardiographic patterns of Fallot's pentalogy and transposition of the great vessels which we have not yet described are detailed below.

The electrocardiographic findings in Fallot's pentalogy being quite similar to those previously described in Fallot's tetralogy makes a differential diagnosis between the two diseases extremely difficult. There are certain cases, however, in which the following signs make us think more of pentalogy than of tetralogy.

1. *Usual findings in Fallot's pentalogy* (*Fig. 9*): (a) There is an initial negativity in V_1 and V_2, i.e., complexes of the qR type with negative T wave. (b) Unipolar morphologies of the left ventricle are found in several left precordial leads. This finding is very unusual in Fallot's tetralogy. (c) There is first degree A-V block, probably related to the atrial septal defect existing in pentalogy. (d) Sometimes there are T-wave and RS-T segment changes similar to those described above in Fallot's trilogy.

In our laboratory, Zuckermann and associates[94] pointed out negative T waves of the "infantile type" in the left precordial leads, and positive T waves in the right precordial leads, signs which, although appearing rarely, are very suggestive of transposition of the great vessels when present. Still other changes in the T wave lead us to suspect the presence of this disease:

2. *Usual findings in transposition of great vessels* (*Fig. 10*): (a) Positive T waves higher on the right than on the left precordial leads, (b) normal positive T waves in V_1 and V_2 with flat T waves in V_5 and V_6, and (c) notching of the T waves on the left side of the precordium.

E. *Cases Located in Sextant IV of Bayley* (*Between +179° and +120°*).—Fallot's tetralogy again heads the list of anomalies within this sextant. Fallot's trilogy was found 3 times less frequently in incidence than was tetralogy. No cases of tricuspid atresia were found in this sextant. The other anomalies which also may be found in this location, but with a very low incidence, are transposition of the great vessels, Fallot's pentalogy, common trunk, single ventricle, and persistent common atrioventricular canal. The only electrocardiographic pattern lacking description is that of common trunk. Its features are described as follows:

Frequent findings in common trunk (*Fig. 11*): (a) High, peaked, and symmetrical T waves are recorded in Leads I, II, V_5, and V_6. (b) Complexes of the qRS or qRs type in V_5 and V_6 are very similar (but with lower voltage) to those seen in ventricular septal defect and persistent common atrioventricular canal. (c) The R wave remains high in all precordial leads. There are times, however, when complexes of rS type (belonging to the trabecular zone of the right ventricle) are recorded in one or two leads (V_2, V_3); in these cases the R wave recovers its high voltage in the subsequent left precordial leads. (d) The T wave may be positive in all the precordial leads (more often from V_2 through V_6). In a few cases the T wave is negative in several leads of the precordium. Occasionally the T waves may show notchings in the left precordial leads, making the tracing very similar to that described for transposition of the great vessels.

The differential electrocardiographic diagnosis of common trunk must be established mainly with the group of Fallot's malformations.

F. *Cases Located in Sextant V of Bayley (Between +119° and +60°) [Fig. 1].*—Every cyanotic entity of our series was found in this sextant. Each appears in Table II according to incidence. The electrocardiographic pattern of each was described above.

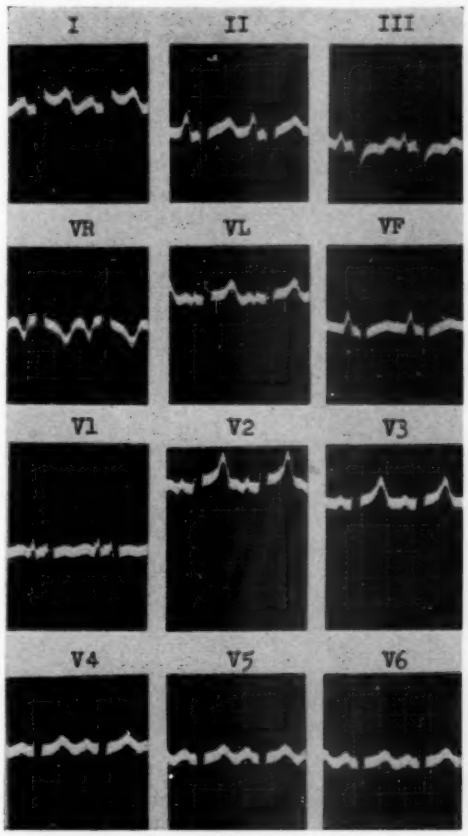

Fig. 11.—Common trunk. Note the relatively tall R waves in the left precordial leads.

CONGENITAL CARDIAC MALFORMATIONS WITHOUT CYANOSIS

A. *Cases Located in Sextant VI of Bayley (Between 0° and +59°). Normal ÂQRS Position (Fig. 2).*—Tracings with ÂQRS located in this sextant correspond principally to patent ductus arteriosus without pulmonary hypertension, and to coarctation of the aorta.

The absence of ÂQRS deviation in patent ductus arteriosus could be due to the lack of pulmonary hypertension; in favor of this explanation we find that a deviation of ÂQRS to the right occurs when pulmonary hypertension is present. The absence of axis deviation in coarctation of the aorta could be related to the concentric type of left ventricular hypertrophy not uncommon in this disease.

It is often necessary to establish the differential diagnosis between patent ductus arteriosus with moderate pulmonary hypertension and ventricular septal defect. The chances are four to one in favor of patent ductus arteriosus when ÂQRS is not deviated (Table II).

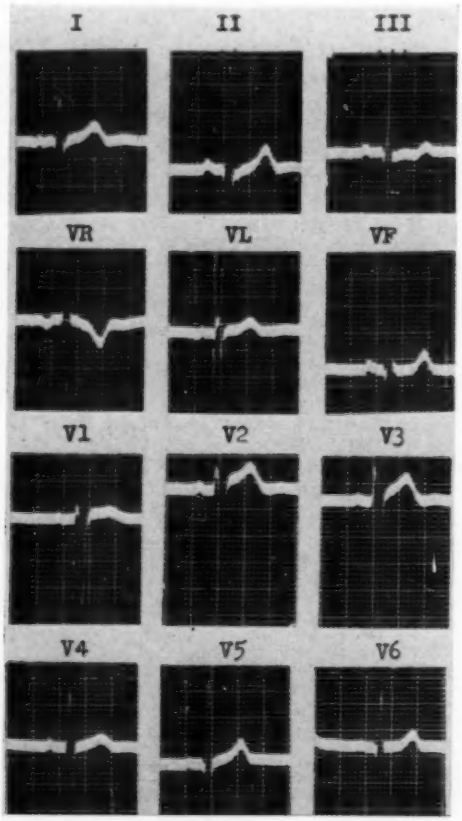

Fig. 12.—Coarctation of the aorta. The electrical axis is not deviated (ÂQRS +60°). Note the deep S waves from V_1 through V_6, and delayed intrinsicoid deflection in V_6.

Congenital aortic stenosis, pure pulmonary stenosis, and atrial septal defect are 3 acyanotic entities also found in this sextant.

The electrocardiographic patterns of the 6 malformations found in Sextant VI of Bayley follow:

1. *Usual findings in patent ductus arteriosus:* (a) There are signs of left ventricular enlargement (diastolic overloading): high R waves with delayed intrinsicoid deflection in V_5 and V_6; high and peaked T waves with or without RS-T elevation, with upward concavity in the same leads; small R waves in the right precordial leads. These signs, when isolated, correspond to patent ductus arteriosus without pulmonary hypertension. (b) There are signs of right ventricular enlargement (systolic overloading): complexes of the Rs or R type with high R waves and negative T waves in V_1 and V_2. When these findings are combined with those described for left ventricular enlargement, i.e., biventricular enlargement, the tracing corresponds to patent ductus arteriosus with moderate pulmonary hypertension. There is a possibility of confusing this pattern with that of ventricular septal defect. When the signs of systolic overloading of the right ventricle

are found isolated, the tracing corresponds to patent ductus arteriosus with high pulmonary hypertension. This tracing may be mistaken for that of pure pulmonary stenosis as well as for that of idiopathic pulmonary hypertension. (c) Large isodiphasic complexes of the RS type with positive T waves in the transitional Leads V_3 and V_4 are observed. (d) There are slight slurrings and notchings in the P waves of the standard leads. The duration of the P waves may reach 0.12 second or more. (e) In a few cases incomplete left bundle branch block is characterized by the T waves remaining positive in the left precordial leads.

2. *Usual findings in ventricular septal defect:* (a) Signs of left ventricular hypertrophy with complexes of the qRs or qRS type in V_5 and V_6 are noted. The Q wave may be quite deep (7 to 10 mm.), a characteristic which is very unusual in patent ductus arteriosus. Generally, the T wave is positive in the same leads and is high and peaked when the pressure in the right ventricular cavity is below 60 mm. Hg. (b) There are signs of right ventricular hypertrophy with some degree of right bundle branch block. The complexes in V_1 and V_2 are of the rsR, rR or Rr type. The first positivity is generally high and, since it is synchronous with the Q wave of the left precordial leads, the possibility of septal hypertrophy in this condition has been suggested in our laboratory. In many tracings the T waves remain positive in the right precordial leads, an unusual finding in patent ductus arteriosus. (c) Deep Q waves may be registered in Leads II, III, and V_F, with or without high T waves and positive RS-T displacement with upward concavity. (d) Large isodiphasic complexes appear in the transitional Leads V_3 and V_4.

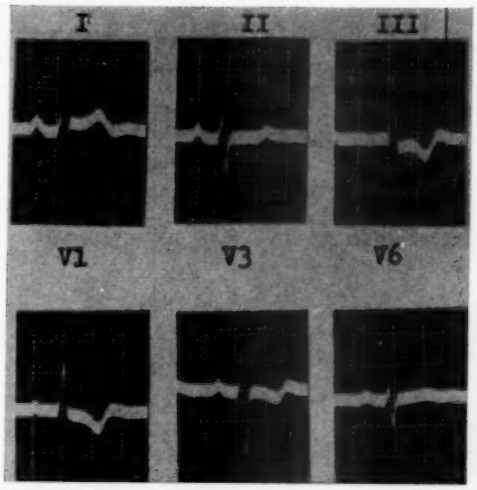

Fig. 13.—Pure pulmonary stenosis with marked right intraventricular pressure. In V_1 the complexes are of the R type with negative T waves. This pattern may be confused with that of patent ductus arteriosus with marked pulmonary hypertension, and with that of idiopathic pulmonary hypertension.

It is sometimes impossible to distinguish the electrocardiographic pattern of ventricular septal defect from that of patent ductus arteriosus.

3. *Usual electrocardiographic findings in coarctation of the aorta (Fig. 12):* (a) The electrical axis (ÂQRS) is not deviated, or it is slightly deviated to the right in 66 per cent of the cases. In the rest, ÂQRS is located to the left of +30°. (b) There are signs of left ventricular hypertrophy: deep S waves in the right precordial leads, delayed intrinsicoid deflection in V_5 and V_6, incomplete left bundle branch block. (c) Few cases show incomplete or complete right bundle branch block.

The pattern of coarctation of the aorta may be confused with that seen in other conditions, such as aortic regurgitation, aortic stenosis, and moderate systemic hypertension.

4. *Usual electrocardiographic findings of pure pulmonary stenosis (Fig. 13):* (a) If the stenosis is small, the tracing is often normal, of the S_1, S_2, and S_3 type, with RS complexes of relatively small voltage in all the precordial leads. The P waves may be normal or slightly peaked. (b) If the pressure in the right ventricular cavity reaches 100 mm. Hg or more, complexes of the Rs, R, qR or rsR are inscribed in V_1 and V_2, sometimes up to V_3 or V_4. The T waves are often positive in the right precordial leads unless the right intraventricular pressure is very high, cases of the ischemic type in which the T waves become negative. In this condition the tracing is quite similar to that of idiopathic pulmonary hypertension. (c) Complexes of the rS type in the left precordium are registered. (d) Peaked and high P waves are found in Leads I and II or II and III.

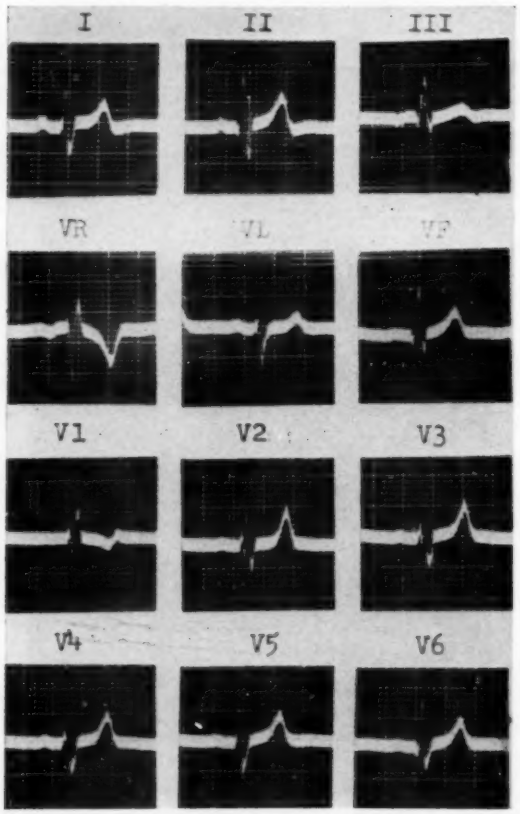

Fig. 14.—Atrial septal defect. Incomplete right bundle branch block is present. The unipolar morphology of the right ventricle is clearly recognized up to V_4.

5. *Usual findings in atrial septal defect (Fig. 14):* (a) Complete or incomplete right bundle branch block is present. The unipolar morphologies of the right ventricle in the presence of the block (rsR, rsRS or RS with initial slurring) are inscribed in most of the precordial leads, sometimes up to V_6, indicating right ventricular enlargement. (b) Slurred and broad P waves in the standard leads suggest left atrial enlargement; there are times when signs of right atrial enlargement (tall and peaked P waves) are also present. (c) There is first degree A-V block.

6. *Usual findings in congenital aortic stenosis:* (a) Frequently there is lack of axis deviation. (b) There is incomplete or complete left bundle branch block. (c) If there is no left bundle branch block, complexes the qR type with secondary negative T waves are common findings in the three standard leads. (d) There is high voltage of the ventricular complexes. (e) P-wave changes suggest left atrial enlargement.

B. *Cases Located in Sextant I of Bayley* (*−1° to −60°*).—We find in this sextant the same malformations as in the previous one; their incidence, however, is different, with coarctation of the aorta in first place (Fig. 2). The electrocardiographic patterns of all these entities have already been described.

C. *Cases Located in Sextant II of Bayley* (*−61° to −120°*).—In first place in this sextant is ventricular septal defect, with Eisenmenger's complex second. It is important to establish the differential diagnosis between these two. The following data for Eisenmenger's complex may be helpful.

Usual findings in Eisenmenger's complex (*Fig. 15*): (a) Many tracings are very similar to those described for ventricular septal defect. (b) There is right bundle branch block with unipolar morphologies of the right ventricle (rsR, rsRS, RS) recorded up to V_5 and V_6. Deep or important Q waves are inscribed in the unipolar leads of the left ventricle (Fig. 15). If the Q waves are absent, the tracing resembles that of atrial septal defect. (c) Signs of right ventricular hypertrophy are present: complexes of the Rs or R type with positive T waves in the right precordial leads. Also, as in cases with right bundle branch block, the Q wave is often important in the unipolar leads of the left ventricle. (d) There are large isodiphasic complexes, similar to those seen in ventricular septal defect, from V_1 through V_4 or V_5. (e) Positive T waves are to be observed in all the precordial leads or in most of them when there is no right bundle branch block.

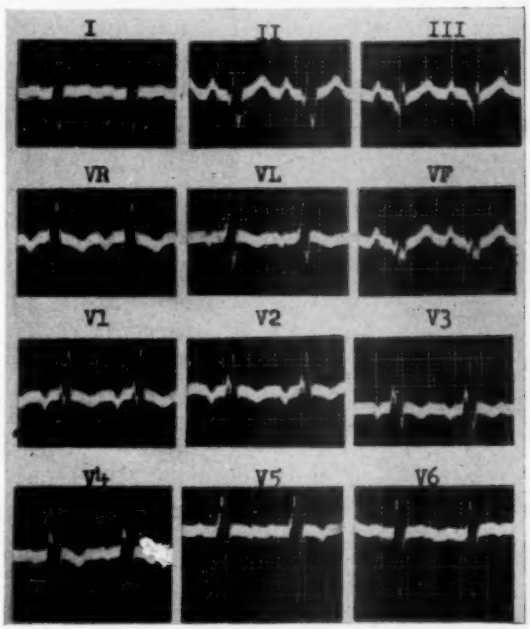

Fig. 15.—Eisenmenger's complex. Incomplete right bundle branch block. The unipolar morphologies of the right ventricle are recognized up to V_6. In Leads II, III, and V_F there are qrS type of complexes with conspicuous Q waves which are very characteristic of potential variations of the left ventricle.

D. *Cases Located in Sextants III, IV, and V* (*Fig. 2*).—The same malformations seen in previous sextants are found, but with different incidence. Their electrocardiographic patterns have already been described.

Table II shows the distribution in the triaxial system of each one of the malformations studied in our series.

We emphasize that it has been the purpose of this paper to discuss only the most frequent cardiac malformations observed in daily practice. Obviously, the description of such entities as Taussig-Bing complex, idiopathic pulmonary hypertension, etc., have not been considered.

Fig. 16 shows the percentual distribution of each particular malformation according to ÂQRS position.

Following are some examples of our approach to interpretation of electrocardiographic tracings in cases of congenital heart disease.

1. The tracing in Fig. 8 was recorded from an 8-year-old boy with marked cyanosis since birth. ÂQRS is located around −135° (Sextant III of Bayley). In this sextant (see Fig. 1) the following malformations should be considered in the diagnosis: Fallot's tetralogy, Fallot's trilogy, persistent common atrioventricular canal, Ebstein's disease, single ventricle, and transposition of the great vessels. Evidently, some of them can be discarded: Ebstein's disease (high R waves in V_1 and V_2 and absence of right bundle branch block rule out this possibility); transposition of the great vessels (T-wave behavior makes this possibility improbable); persistent common atrioventricular canal (an improbable diagnosis because of the absence of right bundle branch block and lack of left ventricular enlargement); single ventricle (absence of predominance of negative and isodiphasic complexes adds to the improbability of this diagnosis). We must focus our attention, therefore, upon Fallot's tetralogy and Fallot's trilogy. The presence of deeply negative T waves from V_1 through V_3, the marked displacement with upward concavity of the RS-T segment in the standard Leads V_F and V_6, and the presence of qrS type complexes in Leads I, V_5, and V_6 speak more in favor of the trilogy than of the tetralogy of Fallot. The diagnosis of Fallot's trilogy was proved by the post-mortem study.

2. The tracing shown in Fig. 5 is from an 18-year-old girl with moderate cyanosis since birth. ÂQRS is located near +140° (Sextant IV of Bayley). The following malformations are to be considered: Fallot's tetralogy, Fallot's trilogy, Ebstein's disease, transposition of the great vessels, Fallot's pentalogy, and common trunk. The presence of an advanced degree of right bundle branch block should focus our attention on Ebstein's disease. The presence of qR type complexes with negative T waves in V_1 and V_2, and qRs complexes with negative or diphasic T waves in V_3, V_4, and V_5, suggests marked right auricular dilatation. The right atrium occupies practically all the anterior aspect of the heart. No unipolar morphologies belonging to the right ventricle (rsR or rsRS) are recorded. The P waves are high and wide in Leads I and II. All these electrocardiographic changes reinforce the diagnosis of Ebstein's disease, as was demonstrated in the post-mortem study.

3. The tracing shown in Fig. 15 was made in a 7-year-old boy with slight cyanosis acquired about 5 years after birth.* ÂQRS is located around −90° (Sextant II of Bayley); therefore the main diagnostic possibilities are ventricular septal defect, Eisenmenger's complex, atrial septal defect, coarctation of the aorta, and patent ductus arteriosus. The precordial leads show the characteristic

*Cases like this with slight cyanosis are considered in the acyanotic group in this paper.

pattern of incomplete right bundle branch block. Coarctation of the aorta and patent ductus arteriosus can be discarded because of the rare occurrence of right bundle branch block in these malformations. Unipolar precordial morphologies corresponding to the right ventricle are recorded up to V_5, and perhaps as far as V_6, suggesting marked right ventricular enlargement with high intraventricular pressure. The diagnosis therefore is focused upon atrial septal defect or Eisenmenger's complex. The presence of deep and wide Q waves in Leads II, III, and V_F, where the unipolar morphology of the left ventricle is recognized, makes improbable the diagnosis of atrial septal defect. Consequently, Eisenmenger's complex is the reliable diagnosis as proved by post-mortem study.

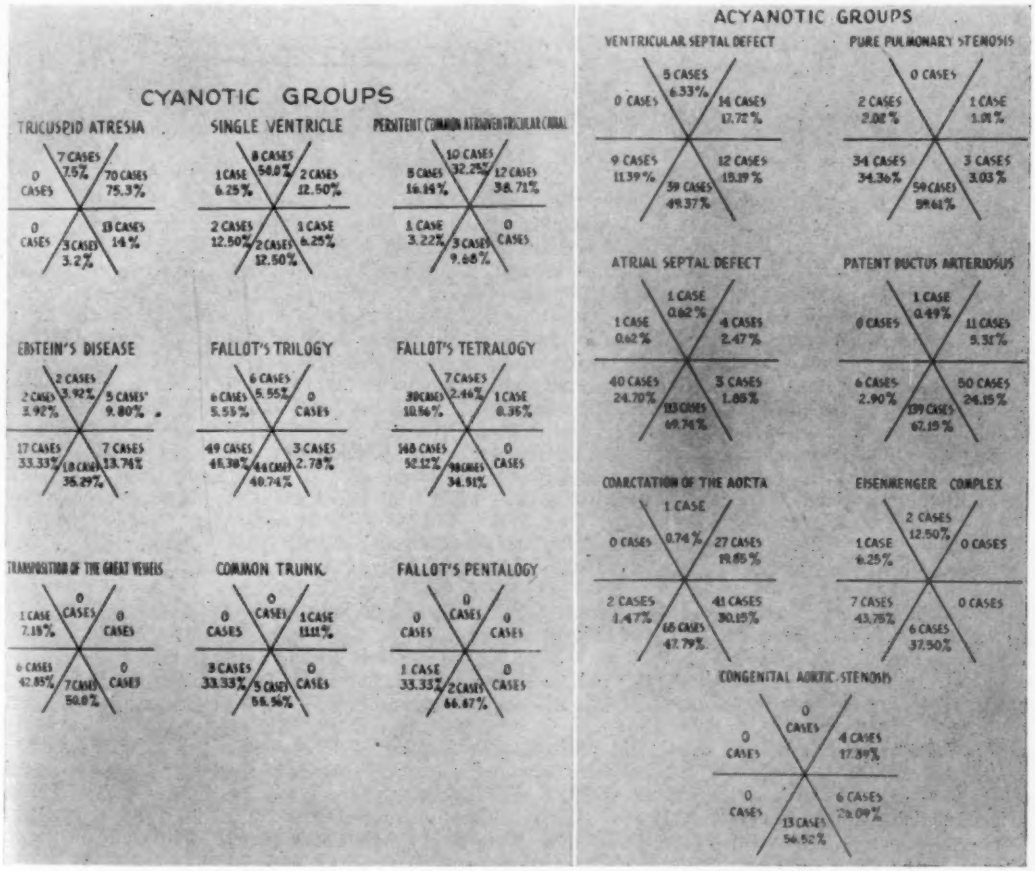

Fig. 16.—Shows the percentual distribution of each particular malformation according to ÂQRS position.

4. The tracing of Fig. 11 was recorded in a 16-year-old girl with marked cyanosis since birth. Since ÂQRS is found around +135°, we must consider the following possibilities: Fallot's tetralogy, Fallot's trilogy, Ebstein's disease, transposition of the great vessels, Fallot's pentalogy, and common trunk. In this tracing it is rather difficult to choose between Fallot's trilogy (marked RS-T displacement with upward concavity in Lead I), Fallot's tetralogy (absence of negative T waves in the right precordial leads and complex of the rS type in V_2,

V_3), and common trunk (due to relatively high R wave, greater than the S wave, in V_5 and V_6.) Fallot's trilogy was discarded because of the absence of negative T waves in the right precordial leads, and Fallot's tetralogy was eliminated because of the presence of tall R waves in the left precordium. In view of the foregoing the diagnosis of common trunk was suggested and proved by x-ray and angiocardiography.

SUMMARY

A new approach in the electrocardiographic diagnosis of congenital heart disease is studied. The combination of the determination of ÂQRS in the frontal plane with the knowledge of the electrocardiographic pattern of each congenital heart malformation permits the main diagnosis of the anomaly in a great number of cases.

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Some Cardiovascular and Fluid Change Effects of Intravenously Administered Diphtheria Toxin in Dogs

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This study was made to determine some of the pathophysiologic effects of myocarditis induced by intravenously administered diphtheria toxin in dogs. Resulting changes in hemodynamics, extracellular-intracellular fluid volume, cation relationships, and glomerular filtration rates were studied.

MATERIAL AND METHODS

Fluid Volume and Muscle Biopsy Studies.—Healthy mongrel dogs were anesthetized with intraperitoneal Dial-urethane, 0.4 ml. per kilogram of body weight, and 0.032 mg. of morphine sulfate. Extracellular and intracellular fluid volume phases were obtained by simultaneous intravenous administration of T-1824, sodium thiocyanate, and deuterium oxide. Plasma samples were obtained at 10 and 90 minutes after injection, for the determination of the respective dilution volumes and for sodium, potassium, chloride, and bicarbonate values.

Approximately 15 to 20 grams of gluteus muscle was excised, rapidly trimmed free of connective tissue, blotted with moist gauze, minced with scissors, and transferred to tared, dry, clean tubes in 2- to 4-gram portions. Water content was determined by drying samples to constant weight. Fat was extracted into petroleum ether. Sodium and potassium contents were determined by flame photometer after the samples were digested in concentrated nitric acid over a steam bath. Chloride was determined by adding silver nitrate with the nitric acid at the time of digestion, followed by microburette titration according to the method of Volhard-Harvey.[1] All determinations were done in duplicate. Muscle distribution of water and electrolytes was calculated by the method of Hastings and Eichelberger.[2] No correction was made for intracellular chloride, since the primary interest was in the degree of change produced by the experimental procedure.

Plasma volumes and thiocyanate spaces were determined by standard methods.[3,4] Deuterium space was measured as previously described.[5]

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TABLE I. CHANGES IN DISTRIBUTION OF INTRACELLULAR SODIUM AND POTASSIUM (MEQ./KG. OF WET MUSCLE)

DOG	INTRACELLULAR SODIUM			INTRACELLULAR POTASSIUM		
	CONTROL	AFTER	CHANGE	CONTROL	AFTER	CHANGE
1	6.1	16.0	+11.9	87.6	83.9	− 3.7
3	12.0	35.7	+23.3	78.4	68.4	−10.0
4	7.0	9.1	+ 2.1	81.9	78.8	− 7.1
5	9.8	3.5	− 6.3	83.1	94.2	+11.1
7	2.5	17.0	+14.5	84.9	96.4	+11.5
8	0	10.2	+10.2	82.8	87.3	+ 4.5
9	10.9	6.8	− 4.1	84.6	80.0	− 4.6
10	9.4	13.5	+ 4.1	84.5	97.1	+13.6
13	10.6	5.6	− 5.0	79.3	90.2	+10.9
	7.6		+ 5.6	83.0		+ 2.9

TALBE II. CHANGES IN DISTRIBUTION OF MUSCLE WATER DERIVED FROM BIOPSY (C.C./KG. OF FAT-FREE MUSCLE)

DOG	TOTAL H_2O CONTENT			EXTRACELLULAR PHASE			INTRACELLULAR PHASE		
	CONTROL	AFTER	CHANGE	CONTROL	AFTER	CHANGE	CONTROL	AFTER	CHANGE
1	748.3	766.6	+18.3	199.0	213.2	+ 14.2	549.3	553.4	+ 4.1
3	751.2	768.6	+17.4	192.8	181.7	− 11.1	558.4	586.9	+ 28.5
4	757.9	769.0	+11.1	188.3	243.8	+ 55.5	569.6	526.2	− 43.4
6	741.2	745.8	+ 4.6	170.1	137.5	− 32.6	571.1	608.3	+ 37.2
7	740.1	740.5	+ 0.5	159.7	70.5	− 89.2	580.4	670.0	+ 89.6
8	733.3	732.4	− 0.9	193.2	91.9	−101.3	540.1	640.5	+100.4
9	752.8	760.1	+ 7.3	172.9	163.3	− 9.6	579.9	596.8	+ 16.9
10	754.7	754.7	0.0	112.0	91.0	− 21.0	642.7	663.7	+ 21.0
13	746.2	745.4	− 0.8	115.6	128.4	+ 12.8	630.6	617.0	− 13.6
			+ 6.4			− 20.3			+ 26.7

TABLE III. VOLUME MEASUREMENTS: CONTROL AND AFTER TOXIN

DOG	T-1824 (C.C.)			THIOCYANATE (C.C.)			DEUTERIUM (C.C.)			WEIGHT CHANGE (KG.)
	CONTROL	AFTER	CHANGE	CONTROL	AFTER	CHANGE	CONTROL	AFTER	CHANGE	
6	630	550	− 80	3,030	2,690	−340	6,370	6,495	+125	−0.2 (1.6%)
7	530	360	−170	2,240	2,145	− 95	5,065	5,230	+165	−0.1 (1.0%)
8	615	480	−135	2,605	2,380	−225	5,000	5,635	+635	−0.0
9	430	475	+ 45	1,735	1,605	−130	3,410	3,210	−200	−0.1 (1.5%)
13	630	620	− 10	2,380	1,580	−800	5,835	6,520	+685	+0.2 (1.9%)
	567	497	− 70 −12.4%			−318 −13.3%			+282 +5.5%	

Four to 10 days later the animals were given diphtheria toxin intravenously. The dosage had been determined previously by trial and error, so that survival for at least 2 weeks usually occurred. Weakness and anorexia were usually present.

Ten to 12 days following administration of diphtheria toxin the previously described studies were repeated under the same conditions, the biopsy being taken from the opposite side. Complete studies in 9 animals were made.

Hemodynamic Observations.—Cardiac outputs were measured by the direct Fick method. Under fluoroscopic observation a catheter was placed in the right atrium and an indwelling needle inserted into the femoral artery. Expired air was collected in a Douglas bag attached via an inspiratory-expiratory valve to a paraffin and wire muzzle fitted with a right rubber dam.

Heparinized blood samples were collected under oil and analyzed for oxygen and carbon-dioxide contents by the Van Slyke manometric technique. Analysis of expired air was made by the Scholander technique.

Determinations in each instance were made at 3 consecutive 30- to 45-minute intervals, and the mean of these 3 values was used.

These 6 studies were repeated under the same conditions after the injection of diphtheria toxin as described above.

*Glomerular Filtration Rates.**—In 5 of the animals on which hemodynamic observations were made, endogenous creatinine clearance rates were obtained in "before" and "after" studies. Urine samples were collected from an indwelling catheter in 30-minute periods after 3 rinses with water and air at the beginning and closing of the periods. Plasma and urine creatinine levels were obtained by standard methods.[6]

RESULTS

Fluid Volumes and Muscle Biopsy Studies Completed in 6 Animals.—In the completed studies on 6 animals there were no significant changes in plasma sodium, potassium, chloride, or bicarbonate concentrations. Mean control and postdiphtheria-toxin values were respectively: plasma sodium, 138.3 and 140.7 mEq./L.; potassium, 3.9 and 4.2 mEq./L.; chloride, 111 and 114 mEq./L.; and bicarbonate, 24 and 24.6 mEq./L.

Changes in the distribution of intracellular sodium and potassium are presented in Table I. There was no consistent change in intracellular potassium. Intracellular sodium increased in 6 instances. The mean gain was 5.6 mEq./Kg. of fat-free muscle, or 74 per cent of the control value.

Changes in distribution of muscle water were relatively consistent, as shown in Table II. There was either no change or a slight increase in total muscle water. However, the extracellular portion of this volume dropped in 6 of the studies, the mean fall for the total group being 20 ml./Kg. of fat-free muscle.

Data obtained from dilution volumes of T-1824 dye, thiocyanate, and deuterium oxide indicated changes in the same direction as shown by the muscle analysis studies (see Table III). There was a consistent fall in both the T-1824 and thiocyanate spaces, and a small net gain in deuterium space, amounting to about 6 per cent. No significant weight change of the animals was noted.

Hemodynamic Observations.—Changes in hemodynamics are summarized in Table IV. Cardiac output fell in 5 of the 6 animals, the mean fall being 22 ml./min./Kg., or 20 per cent below the control mean output of 110 ml./min./Kg.

*We are indebted to Dr. Daniel Bachman for the creatinine determinations.

This change was produced largely by a decrease in oxygen consumption rather than by consistent changes in arteriovenous oxygen differences. Thus, the mean oxygen consumption fell approximately 13 per cent below control values.

TABLE IV. CHANGES IN HEMODYNAMICS. VALUES FOR CONTROL AND POSTDIPHTHERIA STUDIES REPRESENT THE MEAN OF THREE CONSECUTIVE DETERMINATIONS

DOG	CARDIAC OUTPUT (ML./MIN./KG.)	OXYGEN CONSUMPTION (ML./MIN. STPD)	STROKE VOLUME	HEART RATE	MEAN RIGHT ATRIAL PRESSURE (MM. Hg)	MEAN FEMORAL ARTERY PRESSURE (MM. Hg)
D_2 Control	94	43.15	6.8	170	2.5	112
After	46	40.57	4.1	140	7.2	124
D_3 Control	174	58.50	18.8	93	2.7	110
After	96	43.37	8.8	130	4.7	114
D_5 Control	55	39.98	4.7	138	5.2	93
After	43	30.27	2.9	194	3.2	106
D_6 Control	126	46.09	12.0	147	5.7	133
After	82	54.95	5.5	209	5.0	94
D_7 Control	77	55.48	8.0	155	2.4	110
After	178	64.96	14.5	208	3.2	91
B_1 Control	135	55.96	15.2	123	1.1	87
After	84	29.49	9.5	120	−0.3	66
Mean Change	−22	−6.0	−3.4	+29	+0.7	−9

Mean stroke volume showed a greater fall than cardiac output, the mean change being 3.4 ml. per beat, or 31 per cent decrease. This was in part compensated for by an increase in mean heart rate of 20 per cent.

Mean right atrial pressures increased 19 per cent, from 3.3 to 4.4 mm. Hg. Mean femoral artery pressures fell slightly, from 109 to 100.5 mm. Hg.

Glomerular Filtration Rates.—Changes in endogenous creatinine clearances are shown in Table V. There was a significant drop in each instance. The mean decrease was 23.9 ml./min., or 70 per cent of the control value.

TABLE V. GLOMERULAR FILTRATION RATE (C.C./MIN.)

DOG	CONTROL	AFTER TOXIN	CHANGE
D_2	41.5	25.6	−15.9
D_3	57.8	28.3	−29.5
D_5	37.0	7.2	−29.8
D_6	54.1	3.0	−51.1
D_7	45.3	7.0	−38.3

DISCUSSION

The effects of diphtheria toxin on body tissues are well known. Prominent sites of involvement are the heart, kidney, and nervous tissue. Clinical mani-

festations may include rapid pulse, falling blood pressure, heart failure, albuminuria, pyuria, renal casts, and paralysis of some muscle groups as a result of peripheral neuritis.[7] The animals studied in our experiments showed rear extremity weakness, anorexia, and tachycardia.

The heart muscle showed parenchymatous degeneration with swollen granular and hyalinized fibers with loss of striation. The kidneys showed acute toxic changes consisting of cloudy swelling and necrosis of tubular epithelium.[8] These changes were noted uniformly in our studies of fresh post-mortem tissues.

These studies tend to support the concept that diphtheria toxin has cytotoxic effects on heart muscle, skeletal muscle, and renal tissue. Reasonably consistent patterns of response to diphtheria toxin occurred. These consisted of a slight gain of total body water, a significant fall of extracellular fluid volume, and a gain of intracellular water, as evidenced both by direct muscle studies and by volume distribution changes of T-1824 dye, thiocyanate, and deuterium oxide. It is perhaps significant that the percentile decrease of T-1824 space and thiocyanate space correlated so well as reflections of decreasing extracellular fluid volume. Further intracellular changes were shown by an increase of cell sodium content in excess of cell water gain, whereas potassium changes were variable and not considered significant.

While frank congestive heart failure did not develop in these animals, the hemodynamic changes observed were in the same direction as those demonstrated to occur in congestive heart failure in man.[9] Thus, there was an increase in heart rate, a decrease in stroke volume, and a decrease in cardiac output. Right atrial pressures tended to rise and systemic arterial pressures to fall. Similarly, there was a marked fall in glomerular filtration rates, even beyond the level anticipated by a moderate reduction in cardiac output.

SUMMARY

Injection of sublethal doses of diphtheria toxin in dogs resulted in the following changes: (1) a significant decrease of extracellular fluid volume and an increase of intracellular fluid volume, as demonstrated both by tracer dilution methods and by muscle biopsy methods; (2) an increase of intracellular sodium in muscle; (3) a fall in cardiac output, oxygen consumption, and stroke volume, while heart rate and right atrial pressures tended to increase; and (4) a marked fall in glomerular filtration rate.

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Positional and Respiratory Changes in Precordial Lead Patterns Simulating Acute Myocardial Infarction

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Abnormal electrocardiographic patterns may be produced by a variety of factors. Exercise, taking of food, smoking, change in posture, and change in respiratory rate or level frequently affect the T waves and S-T segments.[1-7] In left ventricular hypertrophy, right ventricular hypertrophy, complete or incomplete left and right bundle branch block, and cardiac displacement, QS deflections and/or significant Q waves occur frequently in Leads V_3 and V_4, less often in Leads V_5 and V_6.[8-10] These patterns may suggest myocardial infarction in the absence of an actual lesion.

The purpose of the present report is to call attention to precordial Lead QRS changes which are produced by respiration or slight shift in the position of the exploring electrodes, and which simulate those seen in acute myocardial infarction. Three cases were observed in a period of 6 months, suggesting that this phenomenon is not rare.

Respiratory QRS variations of the magnitude noted in these cases have not been reported previously. Lapin and Sprague,[11] in a case of left bundle branch block, observed that deep inspiration produced a change from a small RR′ complex to a QS deflection in Lead V_5, and Myers[9,12] stated that respiration may alter the initial phase of the QRS complex in the precordial transitional zone.

CASE REPORTS

CASE 1.—M. K. (Beth Israel Hospital #80684), a 60-year-old man, was admitted on Nov. 9, 1956. Following recovery from a myocardial infarction in 1952, his health had been good. Six days prior to admission a fleeting episode of shortness of breath and substernal discomfort occurred with exercise. The day before admission these symptoms recurred and lasted 2 to 3 hours; it was noted that the pulse rate was 120 per minute. The patient was given digitalis and referred to the hospital with a diagnosis of possible acute myocardial infarction.

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On examination the pulse rate was 86 and regular, the temperature was 98.6° F., and the blood pressure was 130 mm. Hg systolic and 70 mm. Hg diastolic. The apical impulse was palpable in the fifth intercostal space, 3 cm. to the left of the mid-clavicular line, and a Grade 1 apical systolic murmur was audible. A chest x-ray showed dilation of the heart and aorta, and clear lung fields.

The first electrocardiogram (Fig. 1,*A*) showed a P-R interval of 0.22 sec., left axis deviation, and Q waves and inverted T waves in Leads I, aV_L, V_5, and V_6. Four days later T-wave changes in Leads I and V_2 to V_6, and the appearance of a Q wave in V_4 (Fig. 1,*B*) suggested the occurrence of acute myocardial infarction. On the tenth hospital day the electrocardiogram showed deeper T-wave inversion in V_3, tiny initial R and deep S waves in V_4, and QS deflections

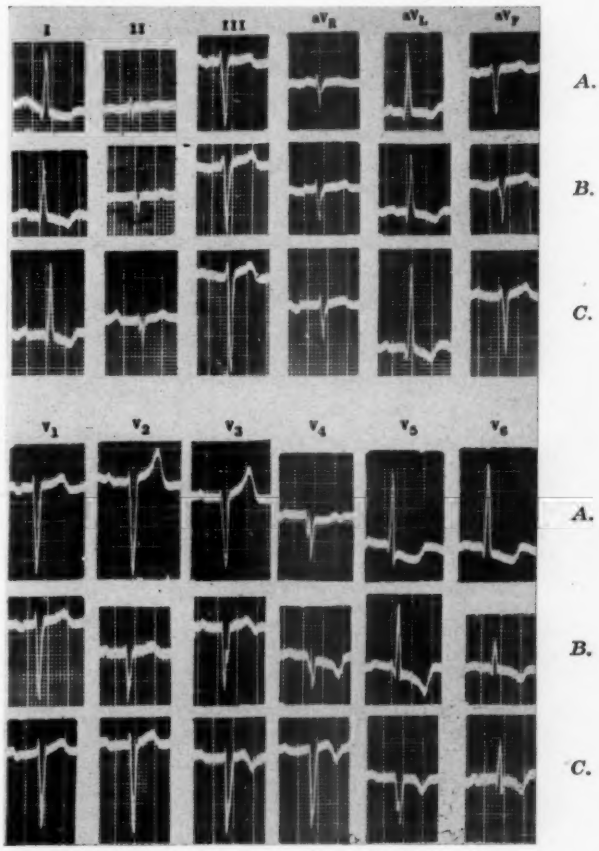

Fig. 1.—Case 1. Serial electrocardiograms with changes suggestive of an acute myocardial infarction. *A*, Nov. 9, 1956. *B*, Nov. 13, 1956. *C*, Nov. 19, 1956.

in V_5 (Fig. 1,*C*). These changes appeared to substantiate the diagnosis of acute myocardial infarction. The clinical picture and laboratory studies, including serial serum transaminase levels, erythrocyte sedimentation rates, and white blood cell counts, were not confirmatory however, and special electrocardiographic studies were carried out.

Slight positional changes of the exploring electrode in the region of Lead V_4 resulted in striking QRS-T changes (Fig. 2). Deep S waves and upright or biphasic T waves were present to the right of the mid-clavicular line and below the fourth intercostal space, and the Q and R waves became larger and the T waves inverted above and to the left of this area. Remarkable changes related to respiration occurred without altering the electrode position (Fig. 3). With deep

inspiration the S waves in Leads V_1 and V_2 became smaller, Q-R-S deflections replaced the deep QS waves in Leads V_3 and V_4, a tall R wave appeared in Lead V_4, and there was a great increase in the amplitude of the R waves in Leads V_5 and V_6. The limb leads showed only minor changes

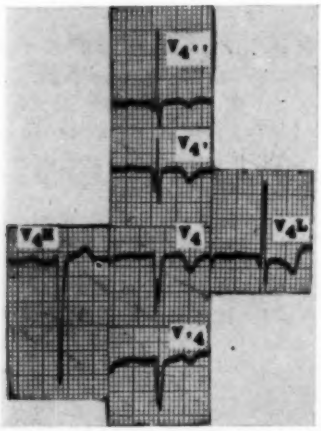

Fig. 2.—Case 1. QRS-T changes secondary to shift of the V_4 electrode. V_4 = standard lead V_4. V'_4 = one intercostal space below V_4. V_4' = one intercostal space above V_4. V_4'' = two intercostal spaces above V_4. V_4M = one inch medial to V_4. V_4L = one inch lateral to V_4.

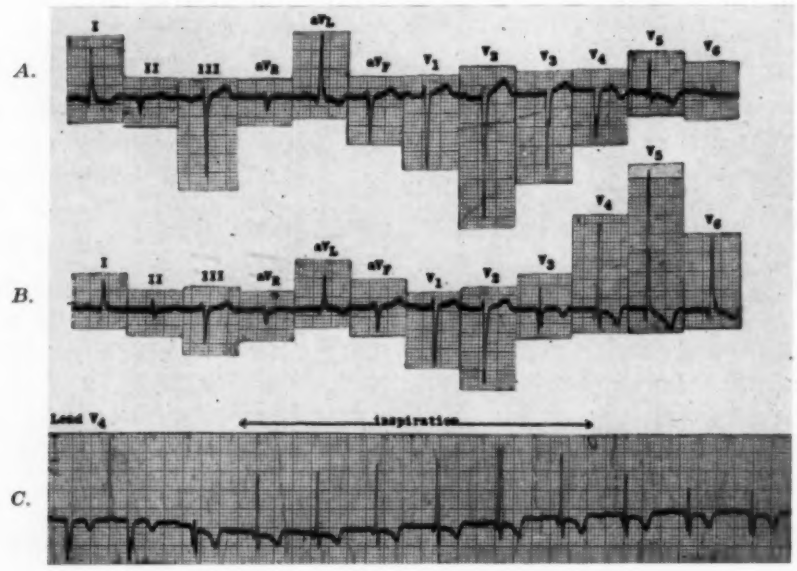

Fig. 3.—Case 1. *A* and *B*, Complexes from a single electrocardiogram without alteration of the electrode position: *A*, Complexes recorded during periods of normal respiration; *B*, complexes recorded during periods of deep inspiration. *C*, Continuous electrocardiogram, Lead V_4, with deep inspiration.

in the amplitude of the QRS complex. Thus, the QRS changes seen in the previous electrocardiograms and interpreted as an acute myocardial process were reproducible by deep inspiration or by slight changes in the position of the exploratory electrode in the region of Lead V_4.

The vectorcardiogram showed slight changes during respiration (Fig. 4). With deep inspiration there was an increase of inferiorly oriented potentials 0.032 second after the onset of depolarization and a decrease of superior potentials toward the end of the QRS loop. The

result was a broadening and shortening of the loop in the sagittal and frontal planes and a slight broadening in the horizontal plane. Serial vectorcardiograms did not reveal intrinsic changes of the kind seen in acute myocardial infarction.

Evidence of acute myocardial disease was not obtained, and the patient was discharged.

CASE 2.—W. R. (Beth Israel Hospital #M85289), a 72-year-old man, was admitted on March 29, 1957, for persistent cough of 4 weeks' duration. For about 1 year substernal pain and dyspnea had occurred with exertion and were relieved by rest.

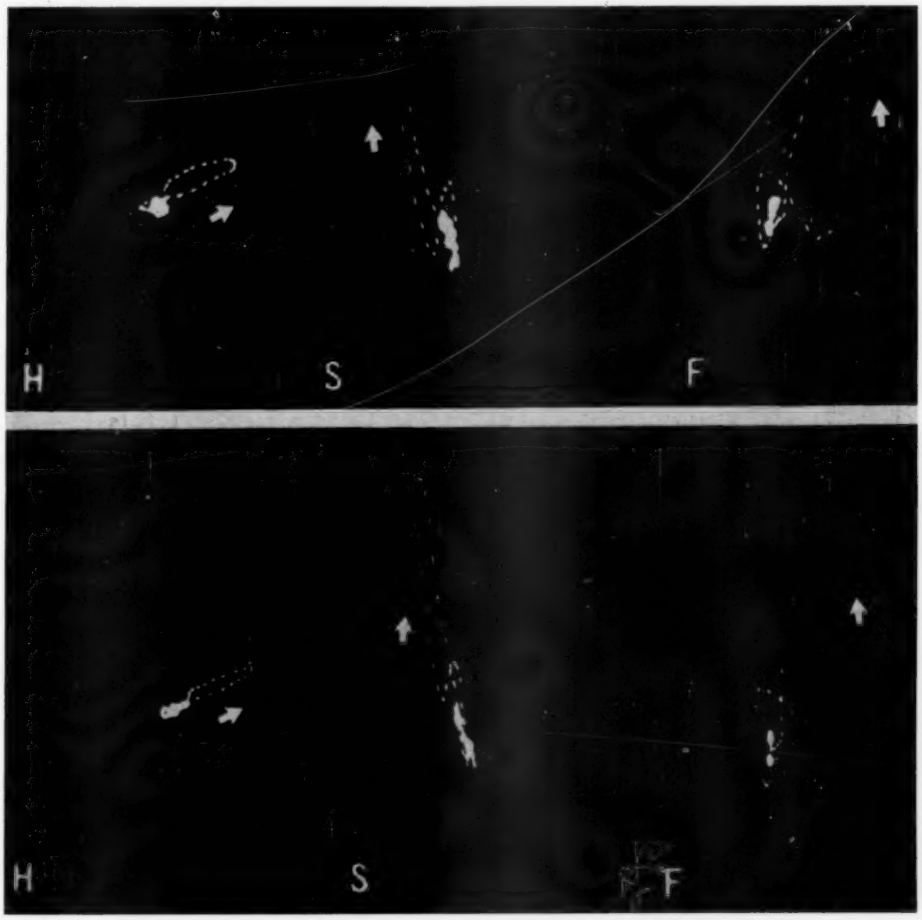

Fig. 4.—Case 1. Vectorcardiograms. Top: during inspiration. Bottom: during normal respiration. *H* = horizontal. *S* = sagittal. *F* = frontal.

Examination revealed a well-nourished man with a frequent nonproductive cough. The blood pressure was 170 mm. Hg systolic and 80 mm. Hg diastolic. The pulse rate was 80 per minute, temperature, 98.6° F. The significant physical findings were a marked increase in the anteroposterior thoracic diameter with poor diaphragmatic excursion, hyperresonance and vesicular breath sounds; a pulsatile, ill-defined mass in the left supraclavicular fossa; deviation of the trachea to the right; a diffuse cardiac apical impulse palpable in the sixth intercostal space at the anterior axillary line; a loud aortic second sound and a soft apical systolic murmur; and distended veins of the left arm and neck.

Pertinent laboratory data included normal urinalyses, a hemoglobin of 14.5 Gm. per 100 ml., and a white blood cell count of 7,300 with a normal differential. The nonprotein nitrogen

was 51 and 63 mg. per 100 ml. Venous pressure in the left and right antecubital veins averaged 85 and 37 mm. of water, respectively. A chest x-ray showed chronic pulmonary fibrosis and emphysema, chronic pulmonary congestion, a sharply defined, round, noncalcific consolidation 2.5 cm. in diameter in the middle lobe of the right lung, marked dilation of the heart, and aneurysmal dilation of the arch and ascending and descending portions of the thoracic aorta.

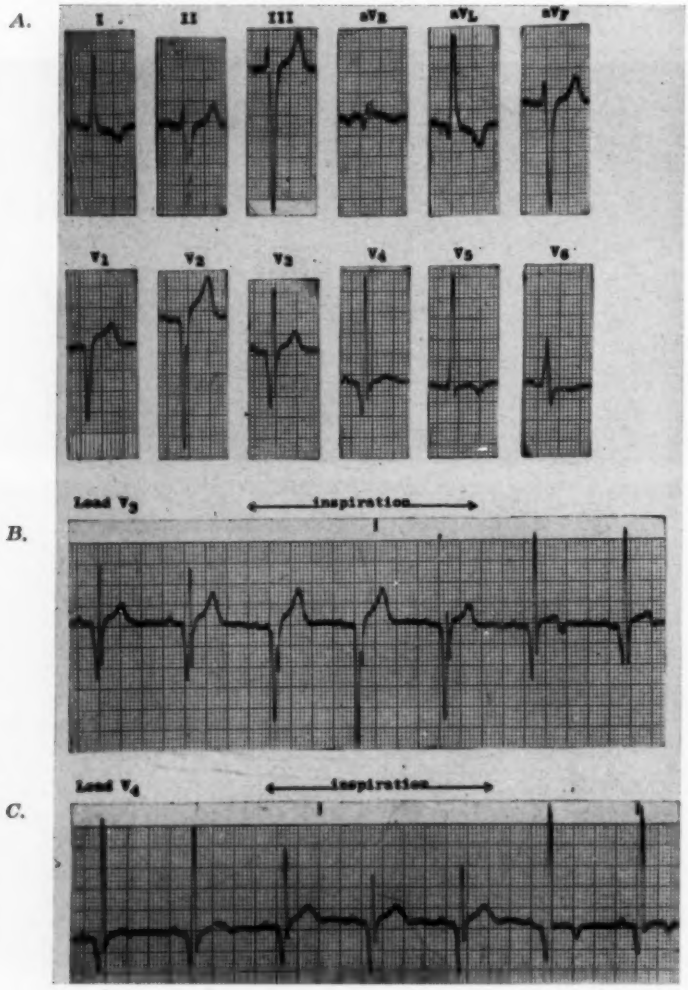

Fig. 5.—Case 2. *A*, Electrocardiogram during quiet respiration. *B*, Lead V_3 during deep inspiration. *C*, Lead V_4 during deep inspiration.

An electrocardiogram (Fig. 5,*A*) showed normal sinus rhythm, rate 70 per minute, left axis deviation, T-wave inversion in Leads I, aV_L, V_5 and V_6, prominent Q waves in Leads aV_L, V_3 and V_4, QS deflections in Leads V_1 and V_2, and S-T segment elevation in Leads V_1 to V_3. On deep inspiration a QS deflection appeared in Lead V_3, the Q wave became deeper, the R wave smaller, and the T waves upright in Lead V_4 (Fig. 5,*B* and *C*).

A vectorcardiogram disclosed a markedly horizontal loop with large superiorly and posteriorly oriented vectors, features characteristics of left ventricular hypertrophy; there were no changes with respiration.

The patient was discharged with a diagnosis of bronchogenic carcinoma.

CASE 3.—S. S. (Beth Israel Hospital #M87708), a 54-year-old man, was admitted on June 6, 1957. There was a history of myocardial infarction in 1947. Left elbow and forearm pain, occurring on exertion and relieved by nitroglycerin, began 2 years prior to admission. For 2½ months he had experienced intermittent episodes of dyspnea and wheezing, particularly when recumbent. The arm pain became more severe and frequent, and often occurred during rest. Five days prior to admission a chest x-ray showed a markedly enlarged cardiac silhouette and pulmonary congestion. Digitalis afforded but partial relief, and the patient was hospitalized.

Examination revealed a husky, comfortable-appearing man. The blood pressure was 160 mm. Hg systolic and 85 mm. Hg diastolic. The pulse was 60 per minute and regular. The temperature was 99.0° F., rectally. The cardiac impulse was palpable in the fifth intercostal space, 8 cm. lateral to the mid-clavicular line. Fine inspiratory râles and prolonged expiration were audible at the left posterior lung base. The liver was felt 4 cm. below the right costal margin.

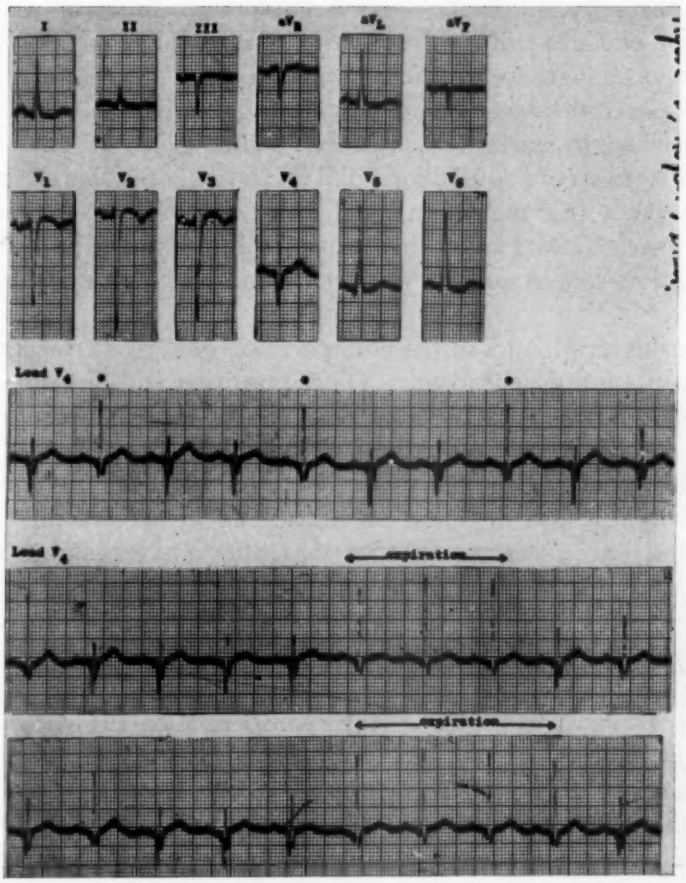

Fig. 6.—Case 3. *A*, Electrocardiogram during quiet respiration. *B*, Lead V_4 during a respiratory rate of 27 per minute; the asterisks indicate the complexes occurring with expiration. *C*, Lead V_4, continuous tracing during slow, deep respiration.

Laboratory data included a normal urinalysis, a hemoglobin of 13.7 Gm. per 100 ml., and a white blood cell count of 9,900 with a normal differential. The sedimentation rate was 37 mm. on entry, 24 mm. 3 days later, and 40 mm. 10 days later. Serum glutamic oxaloacetic transaminase values were 6 units 4 hours following admission, and 4 units 48 hours later.

The admission electrocardiogram (Fig. 6,*A*) revealed normal sinus rhythm at a rate of 80 per minute; left axis deviation; Q waves and shallow diphasic T waves in Leads I, II, aV_L, and V_6; coving of the S-T segments with terminal inversion of the T waves in Leads V_1 to V_3; and Q waves in Leads V_5 and V_6. Restricted to Lead V_4 was a striking continual variation of the QRS complex. A deep Q and tall R deflection appeared with expiration, and an inconstant qrSRS′ complex with inspiration (Fig. 6,*B* and *C*). The number of tall R complexes depended on the respiratory rate; with rapid respiration a single complex occurred, with prolonged expiration there was a series of such complexes.

A vectorcardiogram revealed a horizontally placed loop with marked posterior orientation late in the QRS interval, features characteristic of left ventricular hypertrophy. The early forces were abnormally oriented posteriorly, consistent with the diagnosis of an old anterior myocardial infarction. There were no changes during respiration.

DISCUSSION

In these cases QRS-T changes occurred spontaneously or were induced by deep respiration or slight shift in the position of the exploring precordial electrode. The spontaneous changes were probably related to altered posture, unintentional slight shifts in electrode placement, or involuntary increased respiratory excursion. In Case 1 these slight variations produced striking QRS-T changes leading to an erroneous diagnosis of acute myocardial infarction. Similar changes in Cases 2 and 3 indicate that this may be a much more common error than is generally realized. In Cases 1 and 3 an old myocardial infarction was present, but in Case 2 there was no reason to suspect such a lesion. Cardiomegaly was present in all cases.

The major determinants of the configuration of a given electrocardiographic QRS complex in a unipolar lead are: (1) the position and distance of the exploring electrode in relation to the electrical center of ventricular depolarization ("O" point), (2) the orientation and magnitude of the cardiac vector, and (3) the conducting medium. A change in one or more of these factors will alter the ventricular complex, and all must be considered in attempting to explain the changes effected by respiration. The vectorcardiogram was stable during respiration in Cases 2 and 3. In Case 1 the most significant change was in the superior inferior component of the cardiac vector, but was of minor degree in contrast to the striking electrocardiographic changes. In addition, the respiratory changes were maximal in the mid-precordial leads, not in Leads II, III, or aV_F as would be expected with changes in the vertical component of the vector. It is clear, therefore, that the orientation and magnitude of the cardiac vector were not significantly altered and were not responsible for the electrocardiographic changes occurring with respiration. It is unlikely that alterations in conducting medium secondary to pulmonary aeration are involved, as the electrocardiographic changes were confined to small localized areas overlying the heart and were not accompanied by vectorcardiographic changes.

The position of the exploring electrode in relation to the "O" point remains, then, as the important factor in changing the body-surface potentials produced by electrical activation of the heart muscle in these cases. Whether the change of spatial relationship between the "O" point and the electrode during respiration is due to a shift of the chest electrode secondary to thoracic motion or to a change in the anatomic relations of the equivalent dipole is unknown; both are

probably involved. It is the precordial leads which display the major changes because of their nearness to the "O" point (Fig. 7).

These cases supply clinical support for experimental and theoretical evidence of the importance of considering the position of the "O" point in the interpretation of the precordial electrocardiogram.[14,15] Specific abnormal electrocardiographic patterns may result exclusively from changes in the location of the electrical center of ventricular depolarization. In such cases the electrocardiogram may display a "diagnostic pattern," while the vectorcardiogram remains normal.[16]

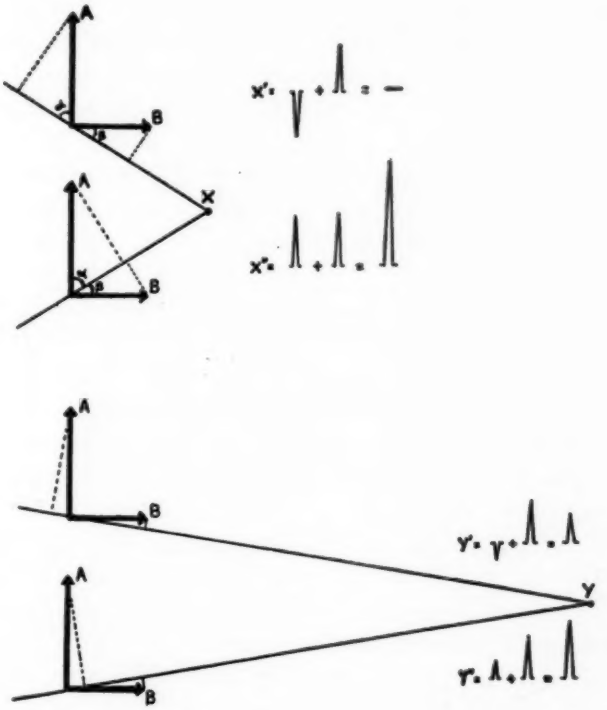

Fig. 7.—Effect of change of the spatial relationship and distance between "O" point and exploring electrode. Electrode X is closer to the "O" point than electrode Y. The amplitude of the QRS deflection is related to K A cos α + K B cos β. With the shift in "O" point position the cosine of α changes markedly for X electrode but only slightly for Y electrode. Thus, a small shift of the "O" point position will affect lead X much more than lead Y. *X'*: Deflection recorded when "O" point is above electrode X. *X''*: Deflection recorded when "O" point is below electrode X. *Y'*: Deflection recorded when "O" point is above electrode Y. *Y''*: Deflection recorded when "O" point is below electrode Y.

Entirely different electrocardiograms can result with identical heart behavior but different heart positions. This aspect of electrocardiography has been almost entirely neglected, despite the fact that its significance was recognized by the pioneers in this field.[1]

These cases also demonstrate the inaccuracy of deriving the precordial electrocardiogram exclusively from the horizontal projection of the spatial vectorcardiogram. This projection remained constant despite marked changes in the precordial electrocardiogram.

Reservation should be exercised in interpreting precordial QRS-T changes, especially when these are localized in the transitional zone. This is clearly shown in Case 1 in which striking changes in Leads V_4 and V_5 suggested acute myocardial infarction. However, these changes could be reproduced at will by slight exploratory electrode positional change or deep inspiration.

SUMMARY

Three cases are presented in which the electrocardiograms displayed precordial QRS-T changes which simulated those of acute myocardial infarction. Electrocardiographic studies disclosed that these changes were produced by respiration or slight shifts of the exploring electrode position.

It is believed that such changes depend upon the position and nearness of the exploring electrode in relation to the electrical center of ventricular depolarization.

Special caution should be observed in interpreting serial changes in precordial leads, especially when they occur in or near the transitional zone.

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The Clinical Significance of Cardiac Gallop Rhythm

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The clinical and prognostic significance of cardiac gallop rhythm has been a matter of interest and of argument since Charcelay[1] first described the phenomenon in 1838. The term "*bruit de galop*" was introduced by Potain[2] for triple cardiac rhythm due to the addition to the first and second heart sounds of an extra sound coinciding with atrial systole. Subsequently, confusion arose when the term was applied to other forms of triple rhythm and even to splitting of the first or second sound. Potain later widened his original concept and defined gallop rhythm as: "un triple bruit du coeur, constitué par l'addition aux deux temps normaux d'un troisième temps étranger à ceux-ci, qui n'est ni un souffle ni un frottement mais un bruit frappé, interposé entre les bruits normaux dans l'un ou l'autre silence."[3] This excludes murmurs and also splitting of the first or second sounds, in which case the two components are of the same quality and intensity and are usually separated from each other by a very short interval. By current convention, gallop rhythm is limited to triple rhythm due to the third sound (protodiastolic or rapid-filling), the fourth sound (presystolic or atrial) or the summation sound (when the third and fourth sounds coincide). Since the discovery of the physiologic third heart sound,[4] the triple rhythm due to this sound in healthy young people has been distinguished from gallop rhythm in patients with heart disease. The triple rhythms due to a systolic extra sound or to the mitral opening snap are generally excluded from the category of gallop rhythm.

Quadruple rhythm due to the presence of both third and fourth heart sounds has been appropriately named "train-wheel rhythm."[5]

The widely held view that cardiac gallop rhythm is of grave prognostic significance is based more on general impressions than on the critical analysis of series of patients. By modern phonocardiography the different types of gallop rhythm can be identified precisely and the prognostic significance of each can then be ascertained. It is usual to apply the term "heart sound" not only to the audible phenomenon but also to the corresponding audio-frequency vibrations recorded by phonocardiography.

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DETAILS OF INVESTIGATION

Subjects.—One hundred in-patients with definite evidence of heart disease were investigated by phonocardiography at Stobhill General Hospital, Glasgow, Scotland. Forty were male and 60 female, and their ages ranged from 7 to 76 years. As far as possible the cases were unselected, but a few very ill patients were not investigated. Patients with arterial hypertension were included in the series only if there was clinical or electrocardiographic evidence of cardiac abnormality.

TABLE I. DIAGNOSES OF 100 PATIENTS WITH HEART DISEASE

DIAGNOSIS	WITHOUT MYOCARDIAL DEFECT OR DECOMPENSATION	WITHOUT FAILURE BUT WITH MYOCARDIAL DEGENERATION OR STRAIN	IN CARDIAC FAILURE	TOTAL DIAGNOSES
Mitral valve disease only	30	1	3	34
Aortic valve disease only	1	1	2	4
Combined mitral and aortic valve disease	9	3	2	14
Congenital heart disease	5	—	—	5
Angina pectoris	2	2	—	4
Bundle branch block	—	4	1	5*
Myocardial infarction	—	5	3	8
Cor pulmonale	—	4	—	4*
Arterial hypertension	1	19	11	31*
Acute rheumatic carditis	4	—	—	4*
Myocardial degeneration only	—	1	—	1

*Fourteen patients appear in two categories, as follows: One patient with bundle branch block had mitral and aortic valve disease and one had angina pectoris. One patient with cor pulmonale had bundle branch block. Patients with arterial hypertension included one with mitral stenosis, one with aortic stenosis, one with angina pectoris, one with bundle branch block, three with myocardial infarction, and one with cor pulmonale. Two patients with acute rheumatic carditis had mitral valve disease and one had mitral and aortic valve disease.

Table I shows the diagnoses and also the incidence of cardiac failure. From the series, two main diagnostic groups emerge: patients with disease of the mitral valve and patients with arterial hypertension. These groups are sufficiently large to merit separate analysis.

In 29 of the patients with disease limited to the mitral valve there was evidence only of stenosis; in 5 there was evidence of incompetence. All the patients with combined mitral and aortic valve disease had aortic incompetence: in 13 this was associated with mitral stenosis and in 1 with mitral incompetence. Five of the patients with mitral stenosis had undergone valvotomy but are included in the series because they still showed classical signs of mitral stenosis.

Of the 31 patients with arterial hypertension 11 showed signs of cardiac failure, and 16 others had electrocardiographic evidence of left heart strain. Another 3 had myocardial degeneration, and 1 had mitral stenosis.

Phonocardiograph.—The phonocardiograph employed has been fully described elsewhere.[6] The heart sounds are picked up by a chest-piece in which is incorporated a sensitive piezoelectric crystal microphone. The microphone leads to a preamplifier with electronic filters which can simulate the response of the human ear by introducing logarithmic attenuation of the lower frequency vibrations. The preamplifier leads to a standard audio-amplifier, which activates one beam of a double-beam cathode-ray oscilloscope. The phonocardiogram (PCG) is called linear if it is recorded without distortion and logarithmic when the low-frequency vibrations have been selectively attenuated, as by the human ear.[7]

The second beam of the oscilloscope is used for a reference tracing of either the jugular venous pulse or the electrocardiogram (ECG), and a time marking is added by a small lamp flashing 5 times per second.

Procedure.—Phonocardiography was performed with the patient supine and usually with the breath held at the end of expiration. A few dyspneic or confused patients were unable to hold their breath satisfactorily; in these cases breath sounds were recorded, but these were easily identified and did not obscure the heart sounds.

Two logarithmic PCGs and one linear PCG (apical cardiogram) were recorded from the region of the cardiac apex in each case. The first logarithmic PCG was recorded with the ECG and the second with the venous pulse as the reference tracing. The reference tracing for the linear PCG was the venous pulse. Fig. 1 shows records from a patient with classical presystolic gallop rhythm.

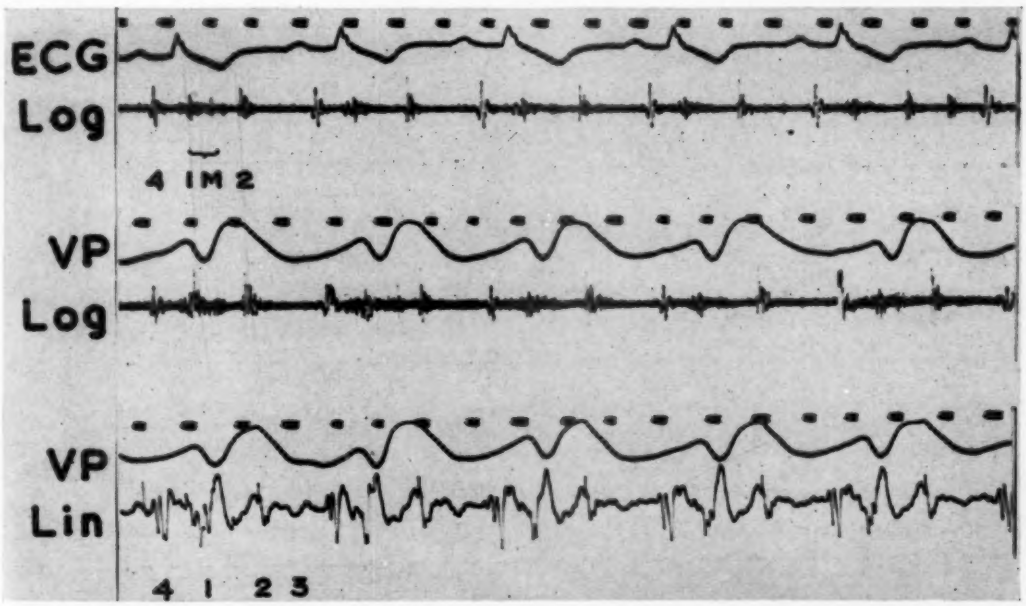

Fig. 1.—Phonocardiograms from the mitral area of a patient with malignant hypertension, myocardial damage, and congestive cardiac failure. *ECG* = electrocardiogram (Lead II). *Log* = logarithmic phonocardiogram. *VP* = jugular venous pulse. *Lin* = linear phonocardiogram. *1, 2, 3, 4* = heart sounds (Log) and corresponding low-frequency vibrations (Lin); *M* = murmur. Time markings are at 1/5 second intervals.

As in previous work on normal subjects,[8] the gain of the amplifier system was so adjusted that, on the photographic record, the deflections corresponding to the first or second heart sound, whichever was greater, were not less than 1 cm. and not more than 2 cm. in amplitude. A cardiac extra sound was deemed to be present if deflections corresponding to the sound appeared in at least three successive cycles on such a record.

The heart sounds in a few cases were so faint that an amplitude of 1 cm. could not be attained without oscillation of the amplifier circuits; such cases were excluded from the series.

Follow-Up.—After 6 to 9 months and after 25 to 34 months, a letter was written to each patient's doctor to ask whether the patient was still alive and, if so, whether his general state of health was improved, unchanged, or worse. In the few cases in which no reply was received the patient or a near relative was asked for the information.

Statistical Analysis.—Analysis of variance was used for the main series and Fisher's exact method[9] for statistical analysis of the smaller groups.

RESULTS

Logarithmic Phonocardiography.—Protodiastolic (third sound) gallop rhythm was recorded on the logarithmic PCG of 15 patients, and presystolic (fourth sound) gallop in 10 patients. Four patients had train-wheel rhythm.

Most of the patients had cardiac murmurs, 3 had a systolic extra sound, and 9 had a mitral opening snap. These findings are not analyzed here but the murmurs and opening snaps supported the clinical diagnoses.

Twelve of the patients with protodiastolic gallop rhythm had disease of the mitral valve, one other was a case of cor pulmonale, and another had congenital pulmonary stenosis; these are all conditions which subject the right ventricle to undue strain. The remaining patient with protodiastolic gallop had arterial hypertension with electrocardiographic evidence of myocardial degeneration.

TABLE II. INCIDENCE OF GALLOP AND TRAIN-WHEEL RHYTHM IN PATIENTS WITH MITRAL VALVE DISEASE AND IN PATIENTS WITH ARTERIAL HYPERTENSION: LOGARITHMIC PHONOCARDIOGRAPHY (78 PATIENTS)

DIAGNOSIS	PROTO-DIASTOLIC GALLOP	PRE-SYSTOLIC GALLOP	TRAIN-WHEEL RHYTHM	NO GALLOP OR TRAIN-WHEEL RHYTHM
Mitral stenosis only	4	1	–	24
Mitral stenosis and aortic incompetence	6	–	1	6
Mitral incompetence without stenosis	2	1*	–	3
Arterial hypertension	2	5	2	22†

*With aortic incompetence also.
†Including one patient with mitral stenosis.

Five of the patients with presystolic gallop rhythm had arterial hypertension complicated by myocardial disease or strain. Of the other 5, 2 had acute rheumatic fever (one with mitral stenosis and the other with mitral and aortic incompetence), 1 had an anterior myocardial infarction, and 2 had left bundle branch block. All these patients, therefore, had some myocardial damage or strain and, in most cases, the left ventricle particularly was affected. Only in the 2 patients with bundle branch block did the P-R interval on the ECG exceed 0.2 second.

Train-wheel rhythm was noted only in old men with left heart strain; in 2 cases this was associated with aortic valve disease, and in the other 2 with arterial hypertension.

In all the patients with cardiac failure, from whatever cause, the incidence of gallop or train-wheel rhythm was not significantly higher than in the patients

without cardiac failure. Neither protodiastolic nor presystolic gallop showed any significant correlation with age, sex, or heart rate.

The incidence of gallop and of train-wheel rhythm in patients with mitral valve disease and with arterial hypertension is shown in Table II.

In the patients with both mitral stenosis and aortic incompetence there was a significantly higher incidence of the third heart sound (protodiastolic gallop and train-wheel rhythm) than was found in cases of pure mitral stenosis ($P < 0.05$). The incidence of the fourth heart sound was not significantly higher in patients with arterial hypertension than in the other cardiac patients.

Linear Phonocardiography.—Vibrations were recorded at the time of the third heart sound on the linear PCG (apical cardiogram) of 75 patients and at the time of the fourth sound in 52 patients, 45 of whom had also third sound vibrations. On such records vibrations below audio-frequency mask the audio-frequency components of the heart sounds, but the linear PCG helps to identify the corresponding sounds on the logarithmic record. The occurrence of vibrations at the time of the third sound on the linear PCGs was significantly related to the presence of this sound on the corresponding logarithmic PCGs ($P < 0.05$). In the case of the fourth sound the relationship was highly significant ($P < 0.001$).

Follow-Up After 6 Months.—Table III shows the result of the follow-up of 100 patients after a period of 6 to 9 months.

TABLE III. FOLLOW-UP OF 100 CARDIAC PATIENTS AFTER 6 TO 9 MONTHS

GENERAL CONDITION	PROTODIASTOLIC GALLOP	PRESYSTOLIC GALLOP	TRAIN-WHEEL RHYTHM	NO GALLOP OR TRAIN-WHEEL RHYTHM
Improved	8	5	1	28
Unchanged	4	2	–	30
Worse	1	3	1	3
Died	2	–	2	8
Untraced	–	–	–	2

In the series as a whole the patients with gallop or train-wheel rhythm did not fare significantly worse than the other patients. In those with a third heart sound (protodiastolic gallop and train-wheel rhythm) there was no significant deterioration relative to the other patients. On the other hand, in the groups with a fourth sound (presystolic gallop and train-wheel rhythm), although less than half had deteriorated in 6 to 9 months, their progress was significantly worse than that of the other patients ($P < 0.05$). Of the 2 fatal cases with train-wheel rhythm one died 3 months and the other 7 months after this rhythm had been detected.

None of the patients with mitral stenosis as the only valvular lesion died, and most improved during the 6 to 9 months whether or not gallop rhythm had been present and whether or not valvotomy had been performed. Although all the patients with mitral stenosis and aortic incompetence who died had a third

heart sound, the group was too small for this to be significant. No deaths occurred in the patients with mitral incompetence and there was no significant deterioration in this group. None of the patients with arterial hypertension died; the progress of these patients was not related to the presence or absence of gallop rhythm.

Follow-Up After 2 Years.—The patients were followed up again after 25 to 34 months. Table IV records the condition of those who were traced.

TABLE IV. FOLLOW-UP OF 100 CARDIAC PATIENTS AFTER 25 TO 34 MONTHS

GENERAL CONDITION	PROTODIASTOLIC GALLOP	PRESYSTOLIC GALLOP	TRAIN-WHEEL RHYTHM	NO GALLOP OR TRAIN-WHEEL RHYTHM
Improved	4	5	–	33
Unchanged	6	3	1	19
Worse	–	1	–	2
Died	3	1	3	14
Untraced	2	–	–	3

As in the first follow-up, no significant deterioration was observed in patients who had had gallop or train-wheel rhythm in comparison with the others. After 2 years neither protodiastolic nor presystolic gallop was associated with significant deterioration. One patient with train-wheel rhythm died 11 months after examination, but the condition of the surviving one was unchanged after 2 years.

Three patients with mitral stenosis as the only valvular lesion could not be traced after 2 to 3 years; of the others in this group all were either improved or unchanged, except 3 without any cardiac extrasound who had died. The patients' progress was not significantly related to the presence or absence of gallop rhythm either in these cases or in those with coincident aortic valve disease or in whom the prevailing mitral lesion was incompetence.

Similarly, in the group of patients with arterial hypertension there was no evidence that the presence of either gallop or train-wheel rhythm significantly affected the prognosis.

DISCUSSION

The series of patients investigated cannot be regarded as typical of heart disease as it occurs in the community, or even as typical of what one might expect to find in the wards of a general hospital. The high proportion of patients with mitral stenosis was due to the hospital bringing in known cases of mitral stenosis for assessment of operability. The second largest group in the series was that of patients with arterial hypertension and cardiac disease or strain. The size of this group also may be ascribed, at least in part, to artificial selection, since some of the patients were brought into hospital for treatment with ganglion-blocking drugs.

The fact that protodiastolic gallop rhythm occurred principally in association with lesions which throw an excessive load on the right side of the heart links up

with the observations of Evans[10] and Miles,[11] who regarded it as a sign of right ventricular failure. In the present series, however, it was associated with strain rather than with congestive failure. Rheumatic heart disease has been noted as an etiological factor in protodiastolic gallop by a number of authors.[12-15] Only one of the patients with protodiastolic gallop in the present series had acute rheumatism at the time of investigation, but the majority had lesions attributable to previous rheumatic involvement of the heart.

Most of the patients with presystolic gallop rhythm were suffering from left-sided cardiac strain or from some myocardial defect; this agrees with the findings of most previous workers. The appearance of a fourth sound was not dependent on prolongation of the P-R interval on the ECG, as has been suggested in other cases.[16-20] Of the 5 hypertensive patients with presystolic gallop rhythm 3 showed evidence of chronic nephritis, which Potain[2,3] regarded as the commonest cause of presystolic gallop.

In patients with arterial hypertension the fourth sound was of common occurrence, either in presystolic gallop or in train-wheel rhythm, but it was not significantly commoner in this group than in the other patients. As in the series reported by Weitzman,[21] the fourth sound was not an indication of cardiac failure, either in patients with arterial hypertension or in the cardiac patients as a whole. Gallop rhythm is seldom found in advanced cardiac failure; it seems to be a sign of strain rather than of decompensation. There was no evidence in this series of the association found by Giroux,[22] White,[23] and Hamilton[24] between tachycardia and gallop rhythm.

In view of the evidence that the third sound is associated with strain of the right side of the heart and the fourth sound with strain of the left side of the heart, it is of interest to compare the present findings with those of Toja[25] on patients with congenital heart disease. Toja found the third sound commoner in patients with a left-to-right shunt and the fourth sound much commoner in patients with a right-to-left shunt.

Train-wheel rhythm has seldom been referred to in the literature. Luisada[26] associated it with ventricular dilatation or strain. The 4 patients with train-wheel rhythm in the present series were all elderly men suffering from conditions which would throw an excessive load on the left side of the heart.

No diagnosis of summation gallop was made. In 3 patients noted as having a fourth sound, summation gallop might have been suspected from the logarithmic PCG, but the linear PCG showed separate groups of vibrations corresponding to the third and to the fourth sounds. In only one case is it felt that gallop rhythm diagnosed as presystolic might have been proved to be summation gallop if the third and fourth sounds had been separated by slowing the heart.

Follow-Up After 6 Months.—After 6 to 9 months the condition of patients whose records had shown a fourth sound had deteriorated significantly, relative to that of the other patients. This supports the commonly held view that presystolic gallop rhythm is of grave prognostic significance. The same deterioration was not seen in the patients with a third sound. This agrees with the findings of Mannheimer,[27] Friedländer,[14] and Cossio and Korn,[28] in contrast to White[23] and Frost,[29] who found that protodiastolic gallop has the same ominous signifi-

cance as presystolic gallop. In the younger patients, of course, triple rhythm due to the third heart sound may be physiologic; in the presence of heart disease it is arbitrarily called protodiastolic gallop. Although 2 of the 4 patients with quadruple (train-wheel) rhythm died during the first follow-up period, this sign does not seem to be so grave as was suggested by Laubry and Routier,[30] who affirmed that it presaged death in a few days.

In the patients with mitral stenosis and aortic incompetence the third sound carried a poor prognosis, probably because it indicated incipient right ventricular failure. It had no prognostic significance in the other groups of patients.

In a series of 100 patients with arterial hypertension Miles[11] found no evidence that gallop rhythm was of any prognostic significance. The observations of Weitzman[21] and the results of the present work confirm this. In none of the patients with arterial hypertension who died during the ensuing 6 to 9 months had cardiac extra sounds been detected. Four of the 5 who died showed signs of congestive cardiac failure at the time of the examination and it is quite possible that gallop rhythm, previously present, may have disappeared with the onset of cardiac failure. The whole question of the incidence and significance of gallop rhythm in arterial hypertension requires reinvestigation now that the facilities of modern phonocardiography are available.

Follow-Up After 2 Years.—After 25 to 34 months there was no longer any significant difference between the condition of patients with a fourth sound and that of the other patients in the series, and there was no evidence that the third sound had any grave prognostic significance. This is in contrast to the finding of Bramwell[31] that only 15 of a series of 63 patients with presystolic gallop rhythm were still alive 18 months after its detection, and to the observation of White[23] that 45 of a series of 100 patients with gallop rhythm died within the ensuing 2 years. The commonest variety of gallop rhythm in White's series was protodiastolic gallop. Since these earlier observations depended on auscultation, it may well be that audible gallop rhythm offers a worse prognosis than that detected by phonocardiography. Although 3 of the patients with train-wheel rhythm had died during the ensuing year, the condition of the remaining one was reported as unchanged. This is further evidence against the view that this phenomenon is a terminal event, but the group is too small for statistical analysis.

After 2 years the condition of patients with mitral valve disease and with arterial hypertension was not significantly related to the presence of gallop or train-wheel rhythm. Even in the patients with mitral stenosis and aortic incompetence, protodiastolic gallop had lost its prognostic significance.

It is evident that cardiac gallop rhythm detected by logarithmic phonocardiography is not necessarily of grave prognostic import.

SUMMARY

1. On logarithmic phonocardiography of 100 cardiac patients, protodiastolic (third sound) gallop rhythm was recorded in 15, presystolic (fourth sound) gallop rhythm in 10, and train-wheel rhythm (third and fourth sounds) in 4.

2. Protodiastolic gallop was associated with right heart strain, and presystolic gallop and train-wheel rhythm with left heart strain or myocardial damage.

These phenomena were not related to the age, sex, or heart rate of the patients or to the presence of cardiac failure. In patients with mitral stenosis protodiastolic gallop was commoner when there was associated aortic incompetence.

3. In the whole series, patients with a fourth heart sound (presystolic gallop or train-wheel rhythm) showed significant deterioration relative to the other patients after 6 to 9 months. Of the patients with mitral stenosis and aortic incompetence only those with protodiastolic gallop rhythm showed significant deterioration.

4. There was no significant correlation between the patients' condition after 25 to 34 months and the presence or absence of gallop or train-wheel rhythm at the original investigation. These findings show that gallop rhythm is not of such grave prognostic significance as has sometimes been believed.

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Congenital Stenosis of Pulmonary and Aortic Valves With Patent Ductus Arteriosus

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A case of combined pulmonary stenosis, aortic stenosis, and patent ductus arteriosus is described. The case is of interest because of its rarity, and because of its presentation as predominantly pulmonary stenosis, particularly in the electrocardiogram. A somewhat similar rare lesion of congenital valvular stenosis of pulmonary and aortic valves with atrial septal defect has been described recently by Horlick and Merriman.[1]

CASE REPORT

The patient, a girl who was 19 years old at the time of her last admission, had been examined periodically from the age of 14 years. She had been admitted to hospital on three occasions in this period for dental treatment, and was last admitted because of serious worsening of her effort tolerance.

When first seen at the age of 14½ years, she was known by her mother to have had heart disease since infancy. The mother had not noticed cyanosis at any time, but she thought that

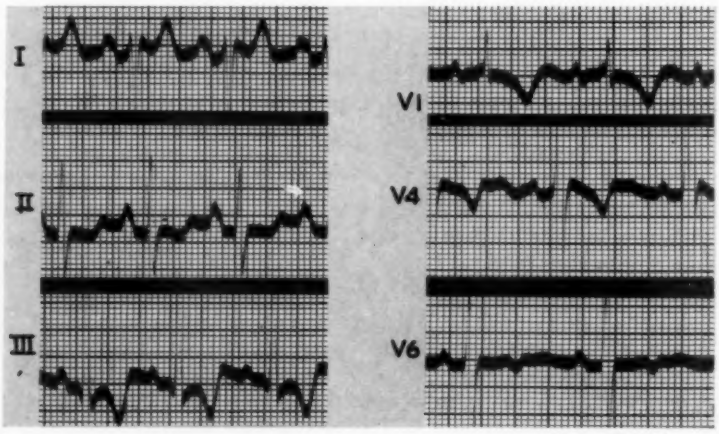

Fig. 1.—Electrocardiogram taken at the age of 14 years. It shows a pattern consistent with severe pulmonary stenosis, but the P waves in Leads I and II were considered unusual.

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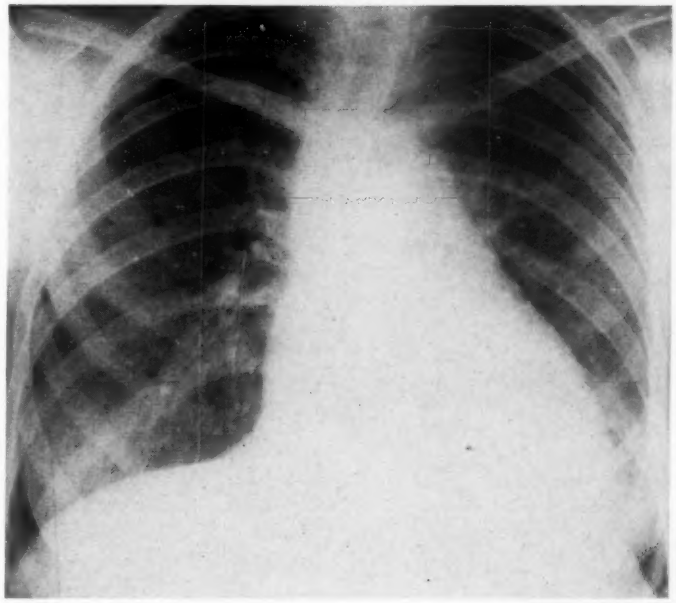
the child was always more dyspneic than the other children. The patient's physical build was normal but there was some degree of mental backwardness. There was no history of illness in the mother during the pregnancy, and eight other children were alive and well.

At the age of 14½ years the patient presented the following clinical signs. She was well-built but with a noticeably plethoric face of high color. There was no cyanosis or clubbing. She



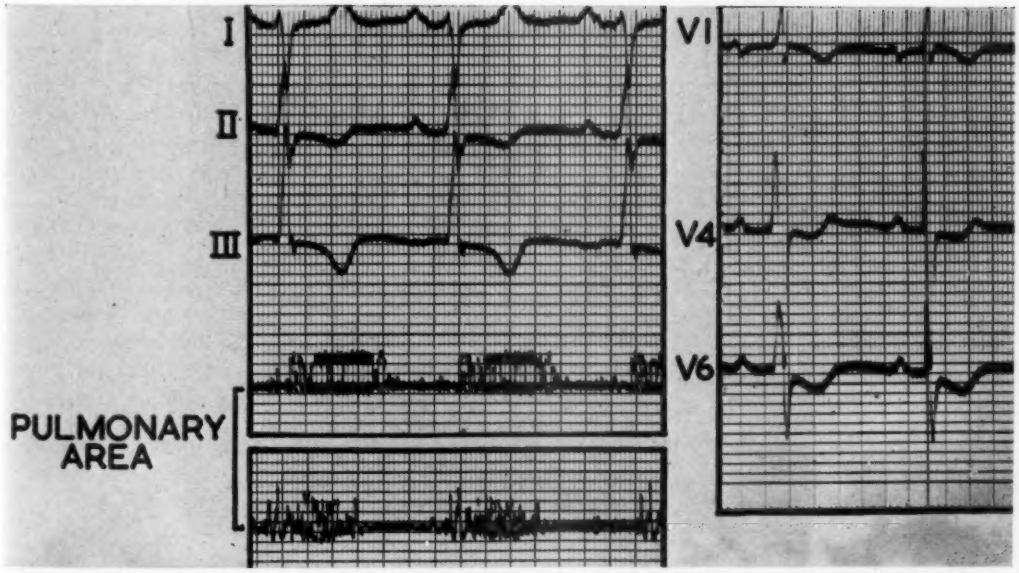


Fig. 2.—The electrocardiogram at age 18 years. The phonocardiogram indicates the loud systolic murmur of the pulmonary area. The radiograph was consistent with a large hypertrophied right ventricle and oligemic lung fields.

Fig. 3.

Fig. 4.

Fig. 3.—The aortic stenosis is indicated. It was of severe degree and there was gross left ventricular hypertrophy.

Fig. 4.—The pulmonary stenosis is indicated. There was extreme narrowing at the valve site but the valve cusps were still separate. The right ventricle was greatly hypertrophied. There was a small patent ductus arteriosus.

had slight kyphoscoliosis, forward curving of the upper sternum, and slight depression of the lower sternum. The heart was enlarged, with an apex beat slightly heaving in character in the anterior axillary line in the fifth intercostal space, and a moderate right ventricular thrust palpable to the left of the sternum. The heart sounds were difficult to hear but the pulmonary second sound was thought to be single. The murmur was a Grade 4 systolic murmur audible perhaps best in the second and third left intercostal spaces, but also well heard over the entire precordium, in the left axilla, over the vessels in the neck and down the arms to the antecubital fossa. No diastolic murmur was heard. The pulse was not collapsing in character, but the blood pressure was recorded as 125 mm. Hg systolic and 60 mm. Hg diastolic, with sounds down to 40 mm. Hg. Cardioscopy at this time recorded a large heart with pulmonary vessels not well seen but regarded as normal, slight left auricular prominence, a large right ventricle (2 plus), and also a prominent left ventricle (1 plus). The skeletal deformity was a possible source of error. The electrocardiogram (Fig. 1) showed severe right ventricular hypertrophy but was a little unusual in the prominence and notchings of the P wave in Leads I and II, with a lower P wave in Lead III, suggesting some left and right auricular enlargement (P congenitale). Apart from a serum cholesterol level which was a little high at this age (205 mg. per 100 ml.) there were no other findings of note.

At the age of 18 years, she appeared below normal in size, slightly retarded mentally, and considerably handicapped by dyspnea on effort. Her mother described occasional attacks of cyanosis on effort, but these were not observed by the author. The clinical signs were mainly unchanged; a second heart sound was still difficult to hear. A phonocardiogram at that time outlined the murmur (Fig. 2), and did show a second sound in the second left intercostal space. The electrocardiogram (Fig. 2) at the same time showed the same prominence of P wave in Leads I and II, and severe right ventricular hypertrophy in the Lead V_1.

She was admitted again the following year with a history of increasing dyspnea on effort sufficient to halt her on one flight of stairs. Her hands and feet became blue in cold weather but further "cyanotic attacks" were not described. There was no history of chest pain, of palpitation, or of transient cerebral attack. The clinical signs had changed little. The pulse was regular but was now thought to have a rather abrupt rise and fall. The blood pressure was recorded as 140 mm. Hg systolic and 40 mm. Hg diastolic, with some sound still audible at 20 mm. Hg. There was a localized thrust at the apex, but the main ventricular thrust was parasternal and right ventricular. The second sound was still poorly heard. Radiologically the pulmonary vessels were regarded as normal, while the heart showed right ventricular enlargement. The dominant lesion clinically was congenital pulmonary stenosis, with discussion of an additional aortic lesion of either slight aortic stenosis or patent ductus arteriosus.

It was decided, wisely or not in retrospect, to submit the case to thoracotomy, in view of the rapid deterioration. At thoracotomy the right and left ventricles were greatly enlarged. There was a gross pulmonary systolic thrill and a gross aortic systolic thrill. The right ventricular systolic pressure was recorded as 120 mm. Hg and the pulmonary artery systolic pressure as 35 mm. Hg. During examination of the left ventricle, irreversible ventricular fibrillation developed and the patient died.

At necropsy the lesions seen were aortic stenosis of severe degree (Fig. 3), with a greatly hypertrophied left ventricle (average wall thickness 25 mm.), an unusual form of pulmonary stenosis with great narrowing of the orifice and pulmonary ring without membrane formation at the site of the valve (Fig. 4), and great right ventricular hypertrophy (18 mm. thickness at a point 2 cm. below the atrioventricular ring). The pulmonary artery was small and divided into its main branches immediately above the pulmonary valve. There was a narrow patent ductus arteriosus running from the pulmonary artery to the aorta.

DISCUSSION

The confusing features were the widespread systolic heart murmur, the consistent widening of the pulse pressure, and the dominant pattern of severe right ventricular hypertrophy. The systolic murmur was due to both valves, and we should have appreciated this fact from the propagation of the murmur.

The recorded pulmonary second sound was a true finding, but the aortic second sound was probably not heard at all. The widening pulse pressure must have been due to the patent ductus arteriosus, although this was small. The presence of a mild degree of pulmonary hypertension supports this explanation. The high right ventricular pressure and the great thickening of the right ventricle is indicative of the pulmonary stenotic lesion.

Pagnoni and Goodwin[2] pointed out that cases with combined hypertrophy may show signs of hypertrophy of one ventricle only on the electrocardiogram. They concluded that cardiographic signs of combined hypertrophy are likely to be seen in only one quarter of the cases.

The P-wave changes, "P congenitale," are referred to by Sodi-Pallares,[3] who also points out that with severe systolic overloading of the ventricle and a right ventricular pressure over 130 mm. Hg in pulmonary stenosis, the ST-T depression and T inversion will be marked from V_1 through V_3. Marquis[4] makes a similar comment. Our case fits with this description except that the changes are more marked than expected in V_6. The best indication of left ventricular hypertrophy in this case was the localized heave of the apical thrust. Clinically it was possible to come to a tentative decision on the lesions in this case if all the findings were considered.

The pathology of the aortic stenosis was the same as that usually found in such valvular stenosis, but the findings in the pulmonary valve were more like those of extreme hypoplasia with a very small valvular orifice but no membrane formed.

SUMMARY AND CONCLUSIONS

A case of combined pulmonary stenosis, aortic stenosis, and patent ductus arteriosus is described. The clinical findings were predominantly those of pulmonary stenosis, but with a widening systemic pulse pressure suggestive of an aorticopulmonary opening. The electrocardiogram recorded in conventional fashion as far as V_6 did not show the presence of an hypertrophied left ventricle, but the conduction of the systolic murmur and the finding of a left ventricular apical heave should have led to earlier clinical recognition of the coexistent aortic stenosis.

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Traumatic Armour Heart

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Two cases of traumatic armour heart have been published by Warburg, one in 1933 and another in 1955.[1,2] In describing the latter case he expressed the belief that such cases are presumably not rare in occurrence, although he found no report of any similar case in the literature.

In 1943, when working as consulting cardiologist at the District Railway Department in Cracow, I had the opportunity to observe a case of traumatic armour heart. For many years I searched in vain for a description of a similar case in the available literature. It was only through Warburg's report published in 1955, that I became acquainted also with his first paper of 1933. This induced me to publish my own case, in spite of the fact that a long time has elapsed since I made my observations, and even though only physical, radiologic and electrocardiographic examinations of the patient were made.

The patient, Joseph S., aged 49, was a railway worker in Bochnia. An x-ray microfilm taken on March 4, 1943, showed an irregular silhouette of the heart. Consequently, on April 17, 1943, an examination of his heart was made.

He reported that at the age of 29, when shunting wagons at the station of Bochnia, he was caught between the buffers and had his chest crushed. He lost consciousness and was taken home in a hopeless state. When he regained consciousness he had very severe pain in the chest, violent dyspnea, and hemoptysis. For 2 weeks his condition was very serious. Edema appeared in the lower extremities and the face. Within 4 weeks the patient's condition improved, so that 2 months after the accident he slowly began to get up. At first he became very exhausted, with edema appearing in the legs and sometimes also in the face. These symptoms disappeared gradually. After 4 months he was able to undertake light work, and after 6 months he returned to his normal work on the railway. At present he is still working and complains of fatigue and difficulty in breathing only during heavy physical efforts.

The constitution of the patient was medium strong; he was satisfactorily nourished. There was sufficient blood supply of the skin and mucosa, and moderate venous stasis in the neck. The thorax was emphysematous.

The heart had a dull sound at the apex, and distinct accentuation of the second sound at the pulmonary artery area. The pulse rate was 80 per minute and regular. During deep respiration it was somewhat accelerated and diminished. The blood pressure was 102/88 mm. Hg. The liver was not palpable.

Electrocardiography.—The electrocardiogram is shown in Fig. 1. The axis was normal (+65°). Sinus rhythm was regular at 83 per minute. Waves $P_{I/II}$ were low, broad, and notched; P_{III} was diphasic (+ −) and notched; P_{CF4} was triphasic (+ − +). P_{II} equaled 0.198 sec.; PQ_{II},

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0.205 sec.; QRS_{III}, 0.09 sec.; and QT_{II}, 0.395 sec. T_I waves were positive and small, T_{II} diphasic (− +), T_{III} inverted, T_{CF4} positive.

Roentgenography.—The roentgenogram (Fig. 2) shows a myopathic heart somewhat enlarged, mainly to the left. In the region of the median arch a sickle-shaped band of calcification is visible. Both diaphragms were flattened during inspiration and both costophrenic angles were occluded.

In the left anterior oblique position (Fig. 3) the heart gives the impression of being small and surrounded by a circular, rather thick band of calcification which also invades the great vessels. The surface of the heart represents in this position a picture of widespread calcification, unequal in intensity, which resembles a geographical map.

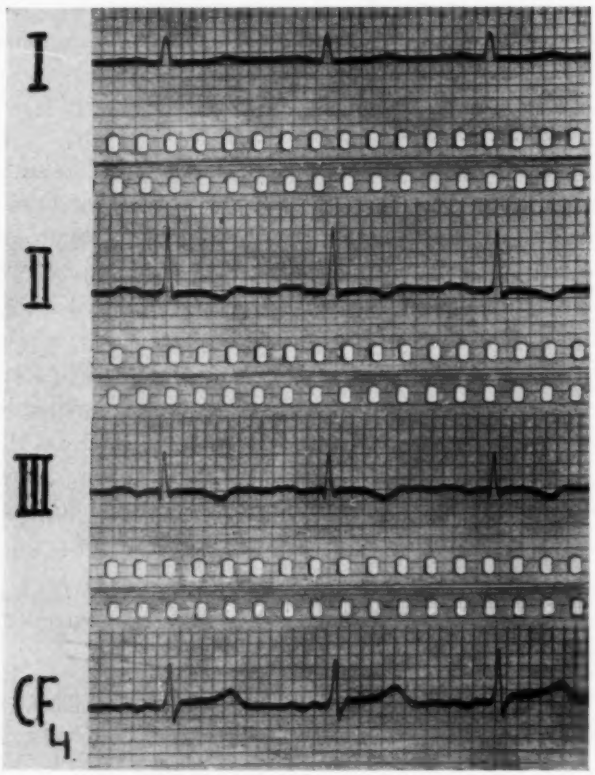

Fig. 1.—April 17, 1943. Normal axis; low, broad and notched P; positive and small T_I; diphasic T_{II}; inverted T_{III}.

This case is of interest because, after very severe trauma, which undoubtedly caused hemopericardium and hemothorax, followed by adhesions and extensive calcifications of the pericardium, as well as by rather extensive pleurodiaphragmatic adhesions, the patient was almost completely fit physically 20 years after the time of the accident. In particular, there were no distinct symptoms such as are usually met with in constrictive pericardial adhesions.

No surgical intervention seems to be indicated in such cases. Twenty years after the trauma, the ECG was typical for such cases, showing broad, notched P waves independent of diphasic or inverted T waves in Leads II and III.

I presume that the rare observation of traumatic armour heart may be due to the fact that an essential condition for its occurrence is very severe trauma which often leads to death, immediately or within a short time after the accident.

Fig. 2.

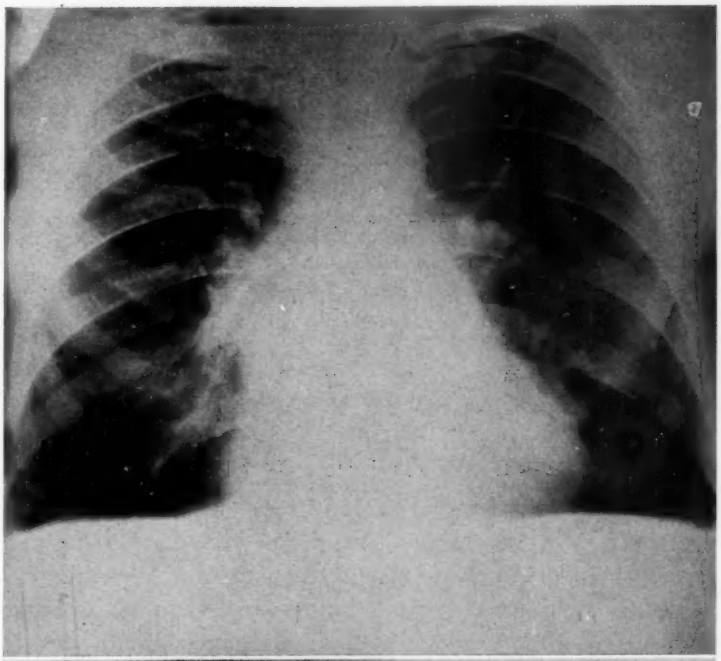

Fig. 3.

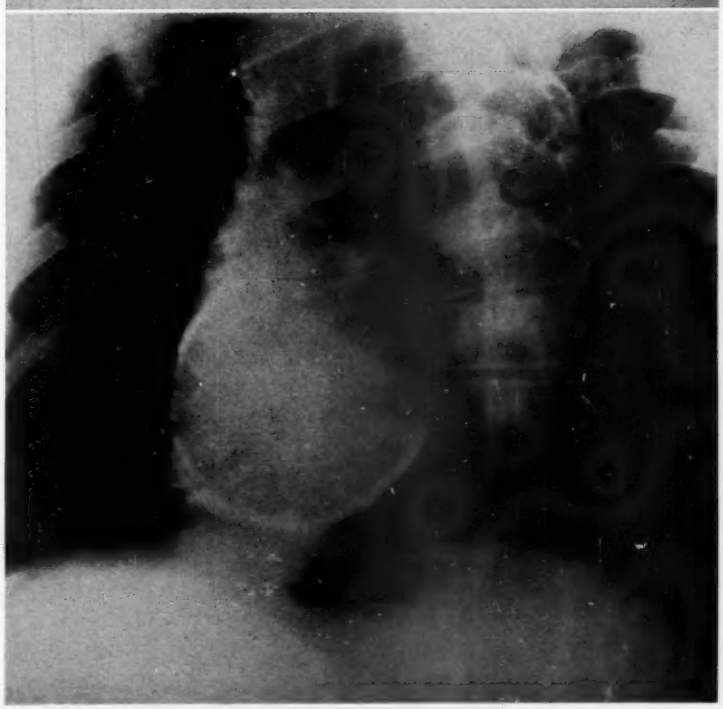

Fig. 2.—April 17, 1943. Myopathic heart, somewhat enlarged, mainly to the left.
Fig. 3.—Left anterior oblique position: widespread calcification of the pericardium unequal in intensity.

SUMMARY

The case is reported of a 59-year-old railway worker who was examined 20 years after severe trauma of the chest. The examination showed the presence of armour heart and rather extensive pleurodiaphragmatic adhesions; physical fitness was almost completely preserved.

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Effect of Hypercapnia on Aconitine-Induced Atrial Fibrillation and on Ventricular Fibrillation Caused by Focal Cooling of the Rapidly Beating Ventricles of the Dog

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The inhibition of ectopic impulse formation by carbon dioxide has gained practical importance with the advent of refrigeration and hypothermia anesthesia. Ventricular fibrillation is one of the commoner hazards of this procedure and its seriousness cannot be overemphasized. It has been stated recently that the danger of experimental ventricular fibrillation could be markedly decreased when the cooled animals inhaled a mixture of 5 to 10 per cent carbon dioxide with oxygen. Similar results have been obtained clinically.[4,9,10]

The study reported in this paper is concerned with the effect of inhalation of carbon dioxide on atrial fibrillation caused by aconitine and on ventricular fibrillation elicited by focal cooling of a rapid heart. Previous experiments have shown that focal cooling of the rapidly beating ventricles leads to ventricular fibrillation.[14]

METHOD

The method was the same as that used in the authors' experiments on the effect of focal cooling. The animals were healthy mongrel dogs weighing between 10 and 14 pounds. They were intubated by means of a tracheal catheter, and artificial respiration was maintained throughout the experiment by an electrical pump which could be connected to any desired mixture of gas. In these experiments the mixture was 20 per cent carbon dioxide and 80 per cent oxygen. The cooling was accomplished by applying a test tube filled with ice to the right ventricle over an area less than one-half square centimeter in size and devoid of visible large coronary vessels. The vagi were severed in the neck. A rapid ventricular rate was produced by the application of a few small crystals of aconitine to the appendix of the right atrium. In less than a minute this led to atrial flutter or fibrillation. All electrocardiograms were registered in Lead II.

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RESULTS

In 7 experiments we studied the effect of the inhalation of the carbon-dioxide mixture on the atrial flutter or fibrillation caused by topical application of aconitine. There was no change either in the time of appearance of these arrhythmias, their duration, or the ventricular response, even when the mixture was inhaled for 10 minutes. This is in contrast to the extrasystoles which appear after minute doses of aconitine injected intravenously, and which are readily abolished by inhalation of carbon dioxide,[12] as are the arrhythmias due to veratrine,[15] strophanthin, and barium.

The data obtained in 15 further experiments are compiled in Table I. In these experiments focal cooling was performed on the right ventricle after 5

TABLE I

DATE OF EXPERIMENT	TYPE OF ATRIAL ARRHYTHMIA, AND RATE, FOLLOWING ACONITINE	INTERVAL BETWEEN ONSET OF CO_2 INHALATION AND COOLING		DURATION OF COOLING (SECONDS)	RESULTS	DURATION OF COOLING NECESSARY TO PRODUCE VENTRICULAR FIBRILLATION, AFTER CO_2 WAS DISCONTINUED FOR 5 MINUTES (SECONDS)
		MIN.	SEC.			
March 26	Flutter 284	5	12	6–18	Sinus rhythm*	
April 2	Flutter 284	5	40	33.8	Ventricular fibrillation	
April 9	Fibrillation 246	9	30	112.8	No changes	
April 16	Fibrillation 260	5	10	108.6	No changes	
April 23	Fibrillation 316	6 10 12 15	36 27 46 30	107 56.4 48.6 51.4	Sinus rhythm Sinus rhythm Sinus rhythm Sinus rhythm	22.6
April 30	Fibrillation 280	6	56	55.4	Ventricular fibrillation	
May 7	Fibrillation 310	6	42	90	Ventricular fibrillation	
May 14	Flutter 210	6	12	56.4	Ventricular fibrillation	
May 21	Fibrillation 276	5	12	94.6	No changes	29.2
June 4	Flutter 276	6	3	59.8	Sinus rhythm	33.8
June 11	Fibrillation 284	5	6	80	No changes	44.6
June 18	Flutter 200	6	40	128.4	No changes	27.6
June 25	Flutter 266	5	50	31.2	Ventricular fibrillation	
Sept. 24	Flutter 284	5	0	106 126	Sinus rhythm No changes	
Oct. 1	Flutter 246	6	0	129	No changes—only sinus rhythm within 30 to 55 sec.	

*Sinus rhythm appeared 6 times within a few seconds during right ventricular cooling.

minutes of inhalation of the carbon-dioxide-oxygen mixture and while aconitine-induced flutter or fibrillation existed. This table shows that in 5 experiments the atrial arrhythmia and ventricular tachycardia remained unchanged until ventricular fibrillation appeared after cooling periods of 31.2, 33.8, 55.4, 56.4, and 90 seconds, while in 7 other experiments focal cooling of the heart for 80, 94.6, 108.6, 112.8, 126, 128.4, and 129 seconds failed to alter the existing rhythm and no ventricular fibrillation developed. In a previous study, cooling in the course of these atrial arrhythmias and high ventricular rates, but without carbon dioxide, led to ventricular fibrillation in 11, 20, 65, 95, and 180 seconds.[13]

Since focal cooling elicited ventricular fibrillation in 2 experiments within 31.2 and 33.8 seconds in spite of carbon-dioxide inhalation, it appears that in these experiments the protection afforded by carbon dioxide is at best uncertain and in some cases completely absent. However, in 5 experiments in which the first cooling failed to produce ventricular fibrillation, the inhalation of carbon dioxide was stopped. After 5 minutes of ventilating with air, the cooling was resumed and in each instance led to ventricular fibrillation within 22.6 to 44.6 seconds.

In 4 experiments sinus rhythm appeared during the cooling. In 3 of these it came quickly and led to a marked slowing of the heart, so that cooling was stopped. Focal cooling rarely leads to ventricular fibrillation when the rate is slow.

DISCUSSION

During focal cooling of the ventricle, single induction shocks applied to a noncooled focus early in diastole cause a repetitive response and ventricular fibrillation originating in the cooled area.[2] Focal cooling of the ventricle without external stimulation may occasionally have the same effect during slow sinus rhythm; however, when the rate is fast, ventricular fibrillation appears more often and more rapidly.[13] In 1 experiment it developed after a cooling of only 6.8 seconds, and it may be stated as a general rule that the faster the rate the earlier the fibrillation.[14]

On the basis of the results obtained in nerve physiology it has been assumed that the repetitive response leading to ventricular fibrillation was due to a number of factors, such as the slowing of accommodation, diffusion of potassium from the cells, reduction of the positive after-potential with increase in the negative after-potential, increase in the excitability with lowering of the rheobase, and local potential differences.[14]

Aconitine-induced extrasystoles in dogs disappeared when the animals were forced to inhale a mixture of 20 per cent carbon dioxide and 80 per cent oxygen.[12] Similar observations were made by Lorente de Nò and Feng[5] working on nerve fibers: the after-discharge produced by barium chloride, sodium citrate, or sodium oxalate was reduced, or ceased, when the nerves were exposed to an atmosphere with a high carbon-dioxide concentration. The explanation given was an increase of the membrane potential and a raised threshold for impulse formation.[5]

It is interesting, therefore, to note the complete absence of effect of carbon-dioxide inhalation on atrial flutter or fibrillation caused by topical application

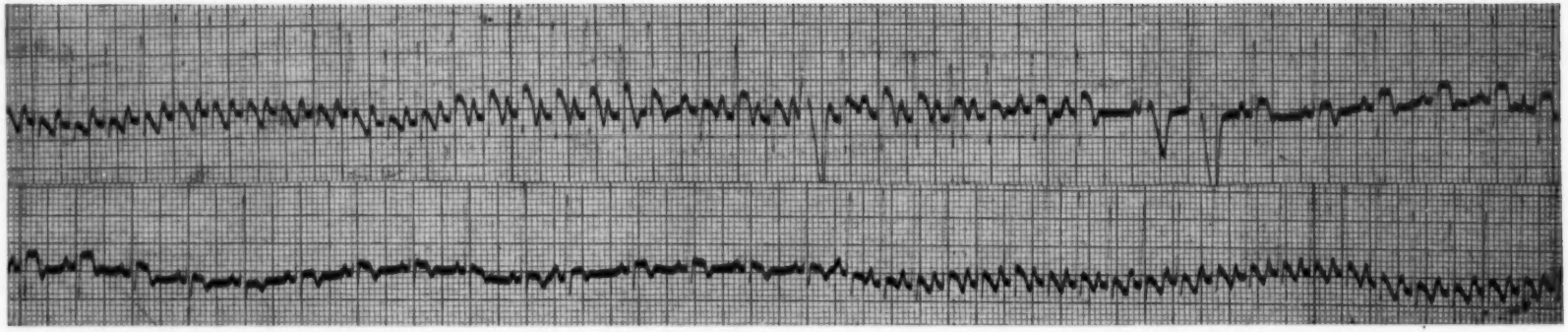

Fig. 1.—Atrial flutter was initiated in the exposed heart of the dog by applying a few crystals of aconitine on the appendix of the right atrium (experiment of March 26). Focal cooling of the right ventricle for 8 seconds leads to the appearance of sinus rhythm (top tracing). In the bottom tracing flutter reappears within 10 seconds after discontinuance of the cooling. The tracings are continuous.

of aconitine. It is probable that this is due to the intense impulse caused by this alkaloid, as compared to the impulse caused by strophanthin, barium, and veratrine.

The relatively common appearance of sinus rhythm during the cooling, and the resumption of the pre-existing arrhythmia within a few seconds after the cooling was discontinued, has already been discussed.[13] We have shown in a previous study that this effect is not due to cooling of the blood since the intracardiac temperatures remain unchanged. In 4 experiments, in addition to severing the vagi in the neck, the sympathetic nerves leading to the heart were also cut bilaterally. In spite of these measures sinus rhythm repeatedly appeared in each experiment upon focal cooling of the right ventricle (Fig. 1). At the present time it cannot be decided whether this phenomenon is due to a release of potassium from the small cooled area. It is known that hypothermia does cause a release of potassium from the cell[3,11] but it is questionable whether the amount released by focal cooling is sufficient to abolish the atrial flutter or fibrillation. The loss of potassium may explain the great flabbiness of the cooled area which appears within about 1 minute after cooling is started.[14] However, after the intravenous administration of aconitine, an intravenous injection of potassium will increase the number of extrasystoles.[12]

Hypercapnia seems to accentuate the loss of potassium which hypothermia initiates in the myocardial cells.[7,8] On the excised Purkinje fibers of the dog the existing rhythm is at first slowed by 10 per cent carbon dioxide, but, when the concentration increases to 20 per cent, double and triple action potentials appear, comparable to bigeminal and trigeminal rhythms, and, finally, a disturbance comparable to a ventricular tachycardia or flutter can be seen.[1] In man, extrasystoles have been seen during inhalation of a 30 per cent carbon-dioxide mixture.[6]

CONCLUSION

In experiments on dogs, inhalation of a mixture of 20 per cent carbon dioxide with 80 per cent oxygen does not alter atrial flutter or fibrillation caused by topical application of aconitine.

Focal cooling on the anterior wall of the right ventricle during aconitine-induced flutter or fibrillation could be extended to more than 2 minutes in some cases during inhalation of carbon dioxide without causing ventricular fibrillation, in spite of a rapid ventricular response. However, in other experiments ventricular fibrillation appeared under the same circumstances as early as after 31.2 seconds. Therefore, in any one experiment the protection afforded by carbon dioxide is uncertain and often entirely absent.

The possibility of a lack of potassium causing flabbiness of the cooled area of the ventricle as well as the temporary disappearance of atrial flutter or fibrillation and the re-establishment of sinus rhythm is discussed.

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An Evaluation of the Serum Glutamic Oxalacetic Transaminase Activity in Pericarditis

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Serum glutamic oxalacetic transaminase (SGOT) has been the subject of extensive investigation since its purification in 1939 and 1940, by Cohen.[1,2] However, this enzyme was of little clinical importance until a simple photometric method for its determination was described by Karmen in 1955,[3] and modified by Henley and Pollard[4] and Ostrow and Steinberg.[5] Nearly all investigators have agreed as to the value of the SGOT levels in myocardial infarction.[6-11] One of the most difficult problems in medicine is the differential diagnosis of myocardial infarction and pericarditis.[12] The nature of the painful episode may be identical; there may be a leukocytosis and rapid erythrocyte sedimentation in both conditions. Electrocardiographic patterns may be similar, particularly in the early period of these illnesses.[12] Accordingly, a reliable method of differentiating these conditions assumes great importance, not only from a prognostic standpoint, but also because of the therapeutic implications. Anticoagulants which are commonly employed and apparently advantageous in acute myocardial infarction are contraindicated and may cause a fatal pericardial tamponade in acute pericarditis. Although there are few data available on the subject of SGOT titers in pericarditis, all authors apparently agree that the levels are usually within normal limits in this condition.[9,13,14]

In a preliminary report, we recently described 2 cases of pericarditis with significant elevation of the SGOT titer.[15] Since that time, we have observed 5 more cases of pericarditis. The purpose of this paper is to evaluate the SGOT levels in 7 consecutive cases of pericarditis, 5 of which were cases of nonspecific pericarditis and 2 of which were cases of myocardial infarction complicated by pericarditis. The clinical data on these cases are summarized in Table I. The following 2 cases are reported in detail to depict the two different types of pericarditis in this series.

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TABLE I. CLINICAL DATA

CASE	AGE (YR.)	SEX	DIAGNOSIS	HIGHEST SGOT TITER (KARMEN METHOD[3])	PERICARDIAL FRICTION RUB	ECG CONSISTENT WITH PERICARDITIS	HISTORY CONSISTENT WITH PERICARDITIS
1.	46	M	Nonspecific pericarditis	75 units	Positive	Positive	Positive
2.	46	M	Nonspecific pericarditis	52 units	Negative	Positive	Positive
3.	38	M	Myocardial infarction and pericarditis	52 units	Positive	Positive	Positive
4.	44	M	Myocardial infarction and pericarditis	56 units	Positive	Positive	Positive
5.	49	F	Nonspecific pericarditis	116 units	Negative	Positive	Positive
6.	34	F	Nonspecific pericarditis	34 units	Positive	Positive	Positive
7.	21	M	Nonspecific pericarditis	165 units	Positive	Positive	Positive

CASE 1.—The patient, a 46-year-old white man, was well until about 9:30 P.M., on July 24, 1956, when he noted the gradual onset of a squeezing pain in the left parasternal area from the second to the sixth intercostal space; the pain was constant but was accentuated from the onset by breathing, sneezing, coughing, or motion of the body, particularly by lying in the left lateral position. There was no associated increased diaphoresis or dyspnea other than that occasioned by shallow, splintered respiration. However, the patient stated that for about 1 week prior to the onset of the pain, he had daily chilly sensations associated with nocturnal elevation of his temperature and generalized weakness.

Past history failed to reveal evidence of cardiac symptoms or of previous involvement of the pericardium.

The patient was first seen at noon on July 25, 1956; at that time, he was extremely apprehensive and was obviously in respiratory distress. There was no evidence of cervical venous distention; a few subcrepitant râles were audible at both lung bases posteriorly. The left heart border was at the mid-clavicular line in the fifth intercostal space. The heart sounds were distant. The aortic second sound was greater than the pulmonic second sound. There was a loud friction rub synchronous with the heart beat, with systolic and diastolic components, maximally audible in the fourth intercostal space at the left parasternal line. The blood pressure was 120/74 mm. Hg, without paradoxical pulsation. There was no hepatomegaly or peripheral edema; all the peripheral pulses were palpated. The temperature was 101° F., by mouth.

The white blood count on entry was 8,500 per mm. with a normal differential; the urinalysis was normal; the erythrocyte sedimentation rate (Wintrobe) was 24 mm. per hour, corrected. The antistreptolysin titer was 100 Todd units. The serum transaminase levels by the Karmen method[3] were 42 units on July 25, 75 units on July 26, and 40 units on July 27. The electrocardiographic tracings revealed a classical evolution of acute pericarditis, with markedly elevated RS-T segments with an upward concavity in Leads I, II, aV_L, and V_3 to V_6, with the absence of reciprocal changes.

The patient's temperature rose to 101°F., by mouth, for the first 2 days; subsequently, the temperature was normal. The pain disappeared in 3 days; the pericardial friction rub persisted for 2 days. Cephalin cholesterol flocculation, thymol turbidity, and serum amylase tests were within normal limits. The patient was discharged from the hospital on the eighth hospital day, afebrile, symptom-free, with only minimal residual elevation of the RS-T segments, and with a normal arm-to-tongue circulation time (15 seconds, Decholin).

CASE 4.—The patient, a 44-year-old white man, was well until about 11:00 P.M., on March 9, 1957, when he noted sudden onset of a severe squeezing substernal pain radiating to the inner aspect of the left upper arm and associated with profuse diaphoresis and moderate dyspnea. The pain was unrelated to breathing, body position, swallowing, or coughing.

There was no past history of cardiovascular disease or recent history of respiratory symptoms.

The patient was first seen about 11:30 P.M. of the night of his acute episode. At this time, he was sitting up, dyspneic, in obvious distress with profuse perspiration. There was no evidence

of cervical venous distention. Lungs were clear anteriorly and posteriorly. The left heart border was 1 to 2 cm. inside the mid-clavicular line at the fifth intercostal space. M1 was weak. The aortic second sound was greater than the pulmonic second sound. No pericardial friction rub or other adventitious sounds were audible. The blood pressure was 100/70 mm. Hg. The pulse was weak but regular at 100 per minute. The remainder of the examination was within normal limits.

The patient was immediately hospitalized. The white blood count on entry was 13,800 per mm.; the erythrocyte sedimentation rate (Wintrobe) was 9 mm. per hour, corrected. The electrocardiogram on March 10, 1957, showed evidence of an acute posterior myocardial infarction. The patient was placed on a regimen for acute myocardial infarction, including the use of anticoagulants; on March 13, 1957, he complained of a new type of lower substernal pain, brought on and accentuated by inspiration and relieved by shallow breathing or breathholding. At this time, a loud pericardial friction rub was clearly audible at the lower level of the left parasternal region, with to-and-fro components. The new pain and friction rub persisted from March 13 to 22, 1957. The electrocardiogram on March 13, 1957, showed elevation of the RS-T segments universally in all leads but aV_R. These RS-T segment shifts gradually reverted to normal by March 22, 1957.

The SGOT titers, the prothrombin time, and the Dicumarol dosages are shown in Table II. Although the exact nature of the pericarditis is not clear, this case may represent another instance of Dicumarol-induced hemopericardium, because of the onset of the clinical pericarditis at the time the prothrombin activity was only 16 per cent, and because of the persistence of the clinical pericarditis for 10 days, an unusual occurrence in pericarditis associated with transmural myocardial infarction.

TABLE II. CASE 4

DATE	PROTHROMBIN TIME (PERCENTAGE ACTIVITY) (QUICK METHOD)	DICUMAROL DOSAGE (MG.)	SGOT TITER (KARMEN METHOD[3])
March 10	85	250	
March 11	49	100	
March 12	24	50	
March 13	16		45 units
March 14	15		39 units
March 15	22		23 units
March 16	27		
March 17	29		
March 18	29		
March 19	31		56 units
March 25	31		31 units

DISCUSSION

These 2 case reports represent 2 different types of pericarditis that we have encountered with elevated SGOT levels. Thus, of 7 consecutive patients observed with pericarditis, 6 had elevated SGOT levels; in 4 of these patients, the maximal level was below 75 units; but in 2 patients the levels exceeded 100 units and were well within the range of levels seen in patients with transmural myocardial infarction. Although there have been no reports emphasizing elevated SGOT titers in patients with pericarditis, there has been adequate experimental basis for this clinical observation.

Agress, Glassner, and Binder[16] produced pericarditis in 13 dogs by using sand talc and cultures of alpha streptococcus. The SGOT titers rose in those

animals in which subepicardial myocarditis was demonstrated histologically; furthermore, those animals with the most extensive subepicardial myocarditis had the highest SGOT titers. The authors concluded that the SGOT titer was only of value in differentiating acute myocardial infarction from pericarditis if the levels were within the normal range.

It has been well accepted that subepicardial myocarditis may occur in pericarditis, and probably accounts for the changes in the electrocardiogram in this condition.[17,18] The failure to report elevated SGOT levels heretofore in pericarditis is somewhat puzzling, but may be due to the failure to obtain blood samples often or early enough or to the absence of significant involvement of the subepicardial myocardium in the reported cases. Since the SGOT titer is elevated in the vast majority of cases with acute myocardial infarction, it would appear that this test is only of value in differentiating pericarditis and myocardial infarction if the levels are within normal limits.

SUMMARY

1. Serum transaminase titers are evaluated in 7 patients with pericarditis.
2. Six of these patients had elevated SGOT levels.
3. Two cases are reported in detail depicting two types of pericarditis with elevated SGOT levels.
4. The experimental basis for these clinical observations is presented.
5. It is concluded that the SGOT determination is only of value in differentiating myocardial infarction from pericarditis if the SGOT level is normal.

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Retrograde Aortography Under Hypothermia in Infancy and Early Childhood

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Retrograde aortography has not been widely employed as a diagnostic adjunct because it has been regarded as more difficult, more time consuming, and more dangerous than angiocardiography, and because it fails to provide information about the heart itself.[1] Aortography is superior, however, in defining the anatomy of a coarctation and in establishing a diagnosis of patent ductus arteriosus or aorticopulmonary fenestration when these diagnoses must be differentiated from each other or from an intracardiac left-to-right shunt. Our present purpose is to describe a method for retrograde aortography under modest hypothermia which improves the technical quality of the result and appears to enhance the safety of the procedure in infants and young children.

MATERIALS AND METHODS

Twenty-seven patients, mostly younger infants, have been subjected to retrograde aortography under hypothermia (Table I). Table II summarizes their pertinent clinical characteristics. Few were cyanotic, inasmuch as aortography is seldom helpful in the diagnosis of cyanotic types of cardiovascular malformation. The high incidence of cardiac enlargement, congestive failure, and growth retardation reflects serious circulatory stresses justifying definitive investigation at earlier than optimal ages. The occurrence of one or more episodes of severe bronchitis or pneumonia in almost one fifth of the group illustrates the high incidence of such complications in infants having left-to-right shunts of large volume which flood the lungs. Table III summarizes the chief differential diagnoses considered prior to special study. The common problem of differentiating the causes of large left-to-right shunts in infancy is evident.

In preparation for the procedure, clear fluids are permitted by mouth until 3 hours before anesthesia, and parenteral fluids are given only as necessary. Scopolamine is usually given before anesthesia, frequently with secobarbital sodium (Table IV). General anesthesia is induced with nitrous oxide and trichlorethylene, supplemented by intravenous thiopental or parenteral meperidine as required. Succinylcholine chloride is given for added relaxation just before tracheal intubation, and again preceding aortography. Hypothermia is induced in an ice bath, or more commonly by the application of plastic bags filled with ice cubes. Table V summarizes the time required to induce hypothermia, the time from first application of ice to retrograde arterial injection,

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the lowest body temperature, and the drift of body temperature after removal from ice. On the average, ice was discontinued at 34°C. after hardly more than one-half hour. Temperature drifted to just under 33°C., and the aortogram was made about 1 hour after induction. We feel that results are most satisfactory when aortography is performed at body temperature, 31 to 32°C.

Table VI summarizes the technique of retrograde aortography. Lead I of the electrocardiogram is monitored continuously. At present, sodium diacetrizoate (Hypaque*) 50 per cent is used

TABLE I. VITAL DATA

Sex:	Male 14	Female 13	
Age:	Range: 2 months to 5 years and 2 months		
	Distribution:	*Number*	*Per Cent*
	Under 1 year	11	41
	1–1½ years	7	26
	1½–2 years	2	7
	2–4 years	6	22
	Over 4 years	1	4
Weight:	Range: 6½ to 37 pounds		
	Distribution:		
	Under 12 pounds	6	22
	12–20 pounds	8	30
	20-32 pounds	11	41
	Over 32 pounds	2	7

TABLE II. CLINICAL CHARACTERISTICS

Cyanosis:			*Cardiac enlargement:*		
Moderate	1	(4)	Present	22	(82)
Slight	2	(7)	Doubtful	1	(4)
Doubtful	3	(11)	Absent	4	(15)
Absent	21	(78)			
Flooded lung:			*Growth:*		
Present	18	(67)	Slow or retarded	13	(48)
Doubtful	3	(11)	Doubtful	3	(11)
Absent	6	(22)	Normal	11	(41)

Respiratory infection:		
Bronchitis or pneumonia at least once	5	(19)
Frequent upper respiratory infection	6	(22)
No unusual history of respiratory infection	17	(63)
Congestive failure:		
Present, compensated	5	(19)
Present, doubtfully or poorly compensated	5	(19)
Suspected, history only	3	(11)
Absent	14	(52)

Percentages are given in parentheses.

*Registered trademark.

TABLE III. DIFFERENTIAL DIAGNOSES PRIOR TO AORTOGRAPHY

Patent ductus arteriosus	25
Ventricular septal defect	21
Aorticopulmonary fenestration	8
Atrial septal defect	6
Coarctation of the aorta	4
Common atrioventricular canal	3
Transposition of great vessels, varieties	2
Endocardial fibroelastosis	2
Others	8

TABLE IV. PREPARATION AND ANESTHESIA

	Number	*Per Cent*
Preanesthetic medication:		
Scopolamine	24	89
Atropine	3	11
Secobarbital	13	48
Penicillin	25	93
Digitalis	8	30
Others	4	15
Parenteral fluids:		
Before or during anesthesia	9	33
Agents used in induction or maintenance of anesthesia:		
Nitrous oxide	26	96
Trichlorethylene	25	93
Thiopental	7	26
Succinylcholine	23	85
Meperidine hydrochloride	5	19
Others	4	15

TABLE V. HYPOTHERMIA

Time in ice:	Range:	13 to 55 min.
	Average:	36 min.
Time from application of ice to injection:	Range:	40 to 130 min.
	Average:	68 min.
Body temperature when ice was discontinued:	Range:	28.0 to 36.5°C.
	Average:	34.2°C.
Lowest body temperature:	Range:	26.0 to 35.5°C.
	Average:	32.7°C.
Drift:	Range:	0.5 to 6.0°C.
	Average:	1.3°C.

as a contrast medium in doses of 0.75 c.c. per kilogram for older patients and 1.0 c.c. per kilogram or more for small infants. At least 10 minutes before aortography an intravenous or intra-arterial test dose is injected (0.5 to 1.0 c.c.). Using the largest metal cannula accommodated by the artery, intra-arterial retrograde injection is made as rapidly as possible under manual pressure while the carotid arteries are firmly compressed bilaterally. The film changer is activated at the instant preceding injection. An Elema biplane roll-film changer was used in all but 2 patients, at a speed of 12 pictures, 10 x 14 inches in size, per second for at least 1 second after injection. Simultaneous posteroanterior and lateral projections are most satisfactory.

TABLE VI. TECHNIQUE

Media:		*Dose:*	
Hypaque:	26	Range:	0.60 to 1.59 c.c./Kg.
Urokon:	1	Average:	0.99 c.c./Kg.
Site of injection:		*Projections:*	
Right brachial artery	20	PA/lateral	20
Left brachial artery	5	Oblique	7
Timing of films:			
1st second after injection, 12 exposures		21/23	
2nd second after injection, 12 exposures		11/23	
2nd second after injection, 6 exposures		10/21	

RESULTS

Table VII summarizes the behavior of body temperature, pulse, and blood pressure under hypothermia. Pulse pressure is included, and "mean pressure" is calculated from diastolic pressure plus one third of pulse pressure. Among these measurements, only heart rate declined significantly under hypothermia, 23 per cent on the average. Methoxamine hydrochloride was given if systolic blood pressure fell below 100 mm. Hg, however, and atropine was administered if the pulse rate declined below 100. Interpretation is necessarily limited, therefore, but these data are consistent with reduction of cardiac output by declining heart rate with little change in stroke volume. Furthermore, a probable decline in volume flow associated with unchanged pressure suggests a proportional increase in peripheral vascular resistance and/or viscosity of the blood.

Effectiveness of contrast visualization is summarized in Table VIII. Results are excellent when opacification is homogeneous, without visible streaming or mixing, and good if visualization is adequate for reliable diagnosis. Aortic sinuses and coronary arteries were commonly but not regularly visualized. The remaining structures of the ascending aorta, arch and descending aorta were quite regularly and reliably observed. At least one internal mammary artery, that on the side of injection, was uniformly well visualized. Hypertrophied collateral circulation was evident in the two clinically significant coarctations. These results are significantly better than those recently reported by Abrams,[2] whose technique was similar except that he used a slower film changer and a different contrast medium, and avoided general anesthesia and hypothermia.

Table IX summarizes the appearance of the aortic isthmus. The isthmus normally narrows somewhat, especially in younger infants.[2] Coarctation as an abnormality is a matter of degree. A constriction or narrowing greater than usual was observed in 3 cases, without clinical significance. Clinically significant coarctation was visualized in 2, and the isthmus was absent or atretic in 1 other.

Table X lists our observations and interpretations of the so-called "ductus diverticulum" and aortic spindle. A definite localized ductus diverticulum was not identified in any patient who failed to show a directly visualized patent ductus arteriosus. A diverticulum was not identified in association with a patent ductus that was identified indirectly in 4 patients by filling of the pulmonary arteries from the descending arch. Diffuse, spindlelike widening of the descending aorta distal to the left subclavian artery was observed in 4 patients with normal aorta and in 2 with patent ductus. A similar observation was interpreted as consistent with poststenotic dilatation in all 4 coarctations.

Table XI lists our diagnoses by retrograde aortogram. The patent ductus arteriosus was visualized directly in half of the 8 patients with this diagnosis. It was always distal to the origin of the left subclavian artery. Coarctations, with or without clinical significance, and various anomalies of the aortic arch

TABLE VII. VITAL SIGNS UNDER HYPOTHERMIA

	CONTROL			OUT OF ICE			AT INJECTION		
	LOW	HIGH	AVER-AGE	LOW	HIGH	AVER-AGE	LOW	HIGH	AVER-AGE
Temperature (C.)	36.5	38.0	37.2	28.0	36.5	34.2	26.5	35.5	33.1
Pulse*	80	190	126	60	155	104	50	174	97
Blood Pressure† (S)	100	185	117	90	170	111	70	170	111
Blood Pressure (D)	40	90	69	40	100	56	40	90	64
Pulse Pressure	20	95	48	30	70	45	30	80	47
"Mean" Pressure	63	122	85	57	110	81	50	117	80

*Usually maintained above 100 by atropine, as necessary.
†Usually maintained above 100 by methoxamine hydrochloride, as necessary.
S and D = systolic and diastolic pressure, respectively, in mm. Hg.

TABLE VIII. OVER-ALL EFFECTIVENESS OF CONTRAST VISUALIZATION

	EXCELLENT		GOOD		POOR OR ABSENT	
Aortic sinuses	1	(4)	11	(41)	15	(56)
Coronary arteries	0		8	(30)	19	(70)
Ascending aorta	6	(22)	17	(63)	4	(15)
Descending aorta	13	(48)	14	(52)	0	
Abdominal aorta	15	(56)	11	(41)	1	(4)
Vertebral arteries	23	(96)	0		1	(4)
Internal mammary	19	(70)	8	(30)	0	
Collateral arteries	2	(7)	1	(4)	0	

Percentages are given in parentheses.

TABLE IX. VISUALIZATION OF AORTIC ISTHMUS

	Number	*Per Cent*
Absent (aortic atresia)	1	4
Coarctation, clinically significant	2	7
Narrowing, constriction or coarctation not clinically significant	3	11
Normal (smaller caliber than ascending aorta, larger than abdominal aorta)	20	74
Not visualized due to dilution	1	4

TABLE X. VISUALIZATION OF "DUCTUS DIVERTICULUM" AND AORTIC SPINDLE

"Ductus diverticulum"		
Patent ductus visualized directly	4	(15)
Possible but doubtful ductus diverticulum	3	(11)
Absent, including 4 PDA demonstrated indirectly only	20	(74)
Aortic spindle		
Coarctation with poststenotic dilatation	4/4	(15)
Present with PDA	2/8	(7)
Present with normal aorta	4/13	(15)
Doubtful, normal aorta	1/13	(4)
Absent, atresia of aortic isthmus	1/1	(4)
Absent, with PDA	6/8	(22)
Absent, normal aorta	9/13	(32)

PDA = patent ductus arteriosus.
Percentages are given in parentheses.

TABLE XI. DIAGNOSES BY RETROGRADE AORTOGRAPHY

	Number	*Per Cent*
Normal aorta	13	48
Patent ductus arteriosus	8	30
Coarctation of the aorta	4	15
Aorticopulmonary fenestration	3	11
Aortic valvular incompetence	2	7
Aortic atresia	1	4

TABLE XII. DIAGNOSTIC RELIABILITY OF RETROGRADE AORTOGRAPHY

Unsatisfactory visualization of pertinent structures		2
Prolonged injection time	1	
Film changer misfire	1	
Diagnostic error		2
True truncus misdiagnosed as aorticopulmonary fenestration	1	
High ventricular septal defect with deformed medial aortic cusp misdiagnosed as aorticopulmonary fenestration with regurgitation into both ventricles	1	

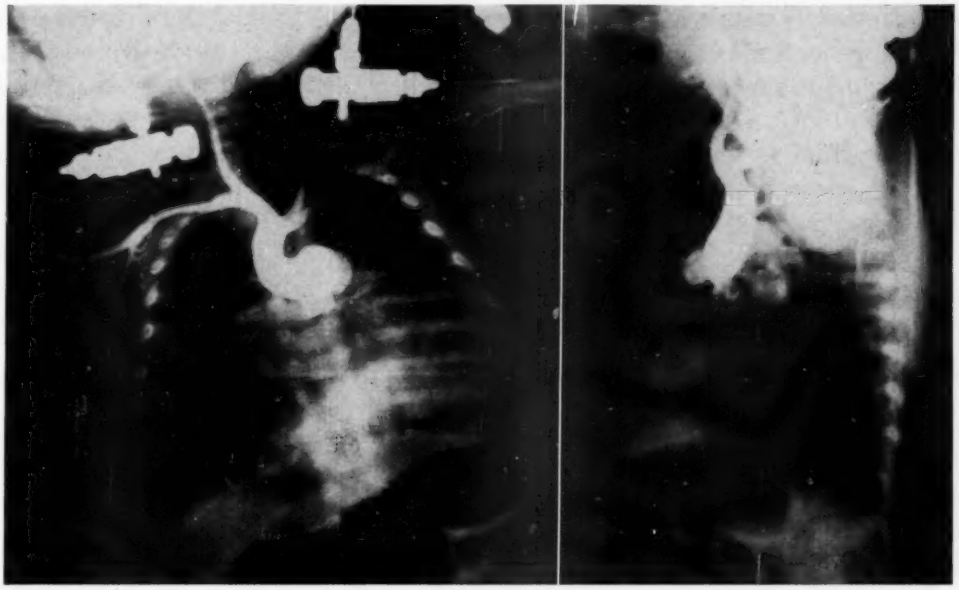

Fig. 1.—Simultaneous posteroanterior and lateral views of a patient with aortic atresia distal to the left subclavian artery. The ascending aorta is well opacified, but the isthmus and distal structures are not seen. Aortic sinuses and coronary vessels are visualized. The pulmonary artery fills from an apparent aorticopulmonary fenestration low and anteriorly.

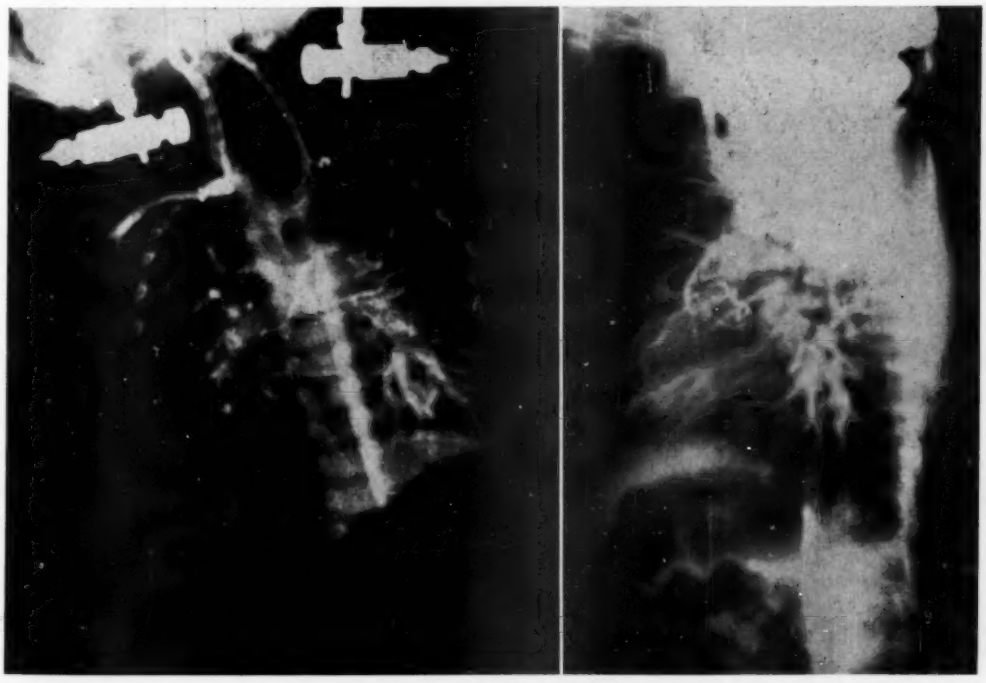

Fig. 2.—Simultaneous posteroanterior and lateral views of same patient as in Fig. 1, one-sixth second later. Isthmus is absent. Pulmonary artery is well filled. Descending and abdominal aorta fill from pulmonary artery.

were graphically demonstrated by aortography. Figs. 1 and 2 show simultaneous posteroanterior and lateral views of a patient whose diagnosis of aorticopulmonary fenestration, absence or atresia of the aortic isthmus, and patent ductus arteriosus was made from the aortogram. The diagnosis was verified at subsequent postmortem examination, with the exception that the apparent aorticopulmonary fenestration was a true truncus arteriosus. Fig. 3 shows another anomaly of the arch in association with coarctation, with poststenotic dilatation and well-developed collateral circulation. Fig. 4 demonstrates a coarctation of no clinical significance. Completing the spectrum, Fig. 5 illustrates a coarctation or constriction so minimal that it might be interpreted merely as a prominent aortic

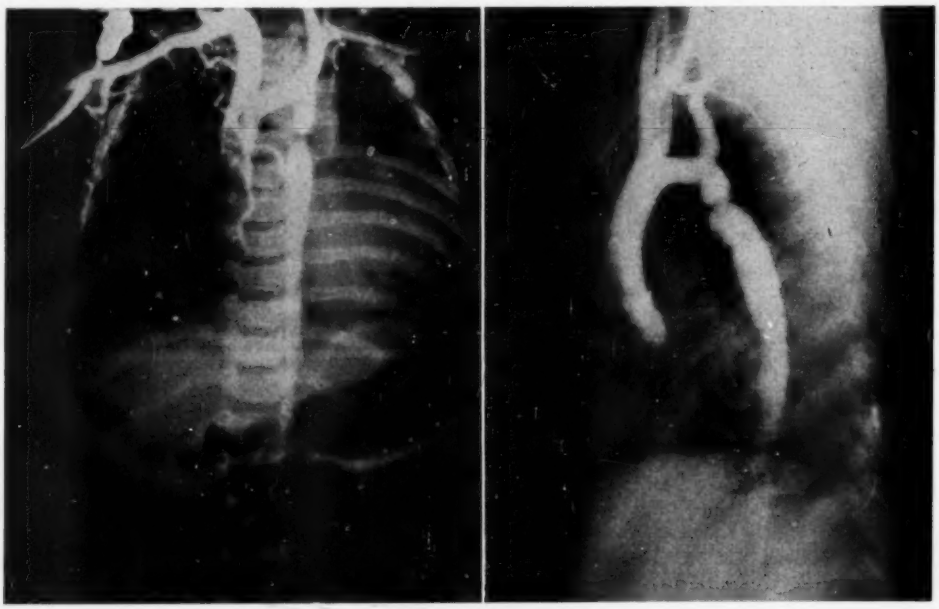

Fig. 3. Fig. 4.

Fig. 3.—Coarctation of the aorta. Collateral circulation is well developed, and the internal mammary arteries are especially dilated and tortuous.

Fig. 4.—Coarctation of the aorta of no clinical significance. Aortic sinuses and coronary arteries are visualized.

spindle. Fig. 6 shows a directly visualized patent ductus arteriosus in comparison with a proved aorticopulmonary fenestration.

Diagnostic errors are listed in Table XII. True truncus was misdiagnosed as aorticopulmonary fenestration in the case of atresia of the aortic isthmus (Figs. 1 and 2), and in a second case where contrast material regurgitated into both ventricles. Autopsy of the latter patient revealed a high ventricular septal defect with deformity of the medial aortic cusp. Sufficient interventricular mixing had occurred to opacify the pulmonary artery, simulating aorticopulmonary fenestration on the aortogram.

Untoward effects and complications are listed in Table XIII. No neurologic complications occurred; visualization of vertebral arteries was uniformly excellent, and frequently there was good visualization of carotid arteries, even with manual compression. Aside from frequent, transient bradycardia following

Fig. 5.—Minimal coarctation with poststenotic dilatation, or normal aorta with prominent aortic spindle.

Fig. 6.—*A*, Patent ductus arteriosus, visualized directly, opacifying pulmonary artery from descending arch. Aortic sinuses and coronary vessels are also visualized. *B*, Surgically proved aorticopulmonary fenestration with opacification of pulmonary artery from ascending aorta.

injection, no rhythmic and no electrocardiographic abnormalities were observed. There were no complications to general anesthesia or to hypothermia. The major complications listed relate to manipulation, but not specifically to aortography. The contracture is listed as preventable because our orthopedic consultants feel that adequate physical therapy might have prevented the problem.

TABLE XIII. COMPLICATIONS AND UNTOWARD EFFECTS

Major:	
Wound infection followed by bacterial endocarditis	1
Difficult arterial dissection, subsequent arterial thrombosis and preventable Volkmann's contracture	1
Minor:	
Slow anesthetic induction and hypoventilation	1
Associated with intubation	
Convulsions	2
Cyanosis	1
Pallor and bradycardia following thiopental and meperidine	1

DISCUSSION

The experience herein reported should not be interpreted as an endorsement for indiscriminate definitive investigation of cardiovascular malformations, particularly in very early life. Clinical angiographic studies are best reserved for problems requiring important diagnostic information not readily obtainable by simpler, safer methods.[3] In infancy and early childhood, however, the pathophysiology of cardiovascular malformations is subject to the influence of circulatory characteristics peculiar to this period of life. Clinical interpretation as well as the evaluation of special diagnostic procedures are often correspondingly more difficult and less certain. The challenge to our diagnostic resources is heightened by increasingly successful cardiovascular surgery during infancy.

Retrograde aortography may yield vital diagnostic information under at least two important and frequent clinical circumstances in infancy and early childhood. In our experience, aortography by the method described far surpasses selective angiocardiography in defining the anatomy of an aortic coarctation. The diagnosis of coarctation may not require angiographic methods, even in early infancy. But the aortogram may be helpful in clarifying its location, extent, and possible functional significance, even under conditions of congestive failure. Significant patency of the ductus arteriosus is usually established or excluded on the same examination. If surgery is under consideration, the value of such information is obvious. The frequency of such circumstances is suggested by the reminder that coarctation of the aorta is among the commonest causes of congestive heart failure in early infancy.[4]

The acyanotic infant with severely flooded lungs and threatened compensation or actual congestive failure presents a frequent and urgent problem. Definitive diagnosis usually cannot be made by simple clinical methods. The experience reported here illustrates the value of retrograde aortography in reliably differentiating patent ductus arteriosus and aorticopulmonary fenestration from intra-

cardiac causes of large left-to-right shunt. The aortogram effectively establishes or excludes the most readily and safely operable possibility, patent ductus arteriosus. The usual first alternative, ventricular septal defect, requires direct proof by other methods. In this series a ventricular septal defect has been demonstrated by cardiac catheterization in several patients whose aortograms failed to reveal the site of the shunt.

Differentiation of patent ductus arteriosus from ventricular septal defect may be accomplished also by cardiac catheterization. This procedure is more time consuming, more expensive, and more difficult, however, particularly in early infancy. Effects of anesthesia and difficulties in achieving a "steady state" may hinder sensitive interpretation of changing oxygen saturation in the right heart and pulmonary artery. As a result, even the cardiac catheter may fail to differentiate a high ventricular septal defect from a patent ductus arteriosus. In addition, successful catheterization of the pulmonary artery is not assured in early infancy.

The value of the cardiac catheter is not to be minimized. However, the merits and disadvantages of each alternative diagnostic procedure should be evaluated for each patient in light of the experience and facilities available. When intracardiac repair of a ventricular septal defect is not under consideration, aortography will differentiate a patent ductus simply and reliably.

Hypothermia adds little to the duration or difficulty of the procedure. In modest degree it can be employed with safety. No significant complications or untoward effects related to anesthesia, hypothermia, or aortography were observed in the present patients. By slowing the circulation, hypothermia appears to minimize dilution of contrast medium, and to lengthen the time of opacification of important structures. The probability of satisfactory diagnostic visualization is enhanced accordingly. Present data suggest that a decline in heart rate approximating 25 per cent indicates sufficient reduction of arterial blood flow for optimum visualization.

SUMMARY

Retrograde aortography under modest hypothermia has been employed in the definitive diagnostic investigation of 27 infants and young children with various congenital cardiovascular malformations. The procedure was most helpful in the study of coarctation of the aorta and in differentiating patent ductus arteriosus or aorticopulmonary fenestration from intracardiac left-to-right shunts which were flooding the lungs. Current experience suggests that hypothermia improves the technical quality of the result by reducing cardiac output and arterial blood flow. The smooth and uneventful character of the procedure and the paucity of untoward effects specifically attributable to it suggest that hypothermia under the conditions described may enhance its safety.

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The Electrocardiogram of a Camel

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INTRODUCTION

The investigations of White and his associates[1] on the elephant have brought forward evidence of a relationship between heart size, heart rate, and time intervals of the cardiac cycle. They have shown that in the elephant the increase of heart size is accompanied by a slow heart rate and lengthening of the P-R, QRS, and Q-T intervals. The fact that the duration of these intervals was out of proportion to the heart rate was explained by the large mass of heart muscle and by the long paths of impulse conduction. In a recent report King, Jenks and White[2] described the electrocardiogram of a beluga whale. Although the heart of this huge animal is much smaller than that of the elephant, its heart rate was found to be about half that of the elephant.

The aim of the present study is to provide additional information on the heart rate and electrocardiographic features in large animals. For this purpose the *Camelus dromedarius* was chosen.

TECHNIQUE OF RECORDING

During the investigation, the camel, a male, weighing 265 kilograms, was in a quiet, sitting position. The usual electrodes were easily placed on the extremities. The tracings were recorded on a direct-writing electrocardiograph, with the standardization 1 cm. = 1 mv. Three bipolar standard limb leads and three unipolar augmented limb leads were obtained. Unipolar chest leads were explored from 20 different positions around the chest in a sagittal plane. In addition, several other points on the shoulders and neck base were explored. The effect of exercise on the electrocardiogram was studied after the camel had walked for a half hour carrying 120 kilograms of weight on its back. Electrocardiographic tracings were similarly recorded, as mentioned above.

GENERAL DESCRIPTION

The chief feature of the electrocardiogram was the sinus bradycardia. The pulse rate ranged between 24 and 30 per minute. This change in the heart rate was due to sinus arrhy-

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thmia. The P waves were well defined, their maximal width was 0.10 sec., and their maximal height 0.2 mv. The P-R interval ranged from 0.24 to 0.26 sec. The P-R segment was isoelectric. The ventricular complexes exhibited small Q waves in some leads and well-defined R and S waves. The maximal duration of the QRS complex was 0.09 sec. and the maximal height was 1.5 mv. No notching or slurring of the ventricular complexes was noted except in Lead I. The direction of the QRS complex was opposite to that of the P wave. The S-T segment was isoelectric. The Q-T interval ranged from 0.54 to 0.60 sec. The T waves were well defined, maximally measuring 0.9 mv. The direction of the T waves was identical to that of the QRS complexes (Fig. 1).

These relationships are illustrated in the frontal projection of the mean P, QRS, S-T, and T vectors (Fig. 2).

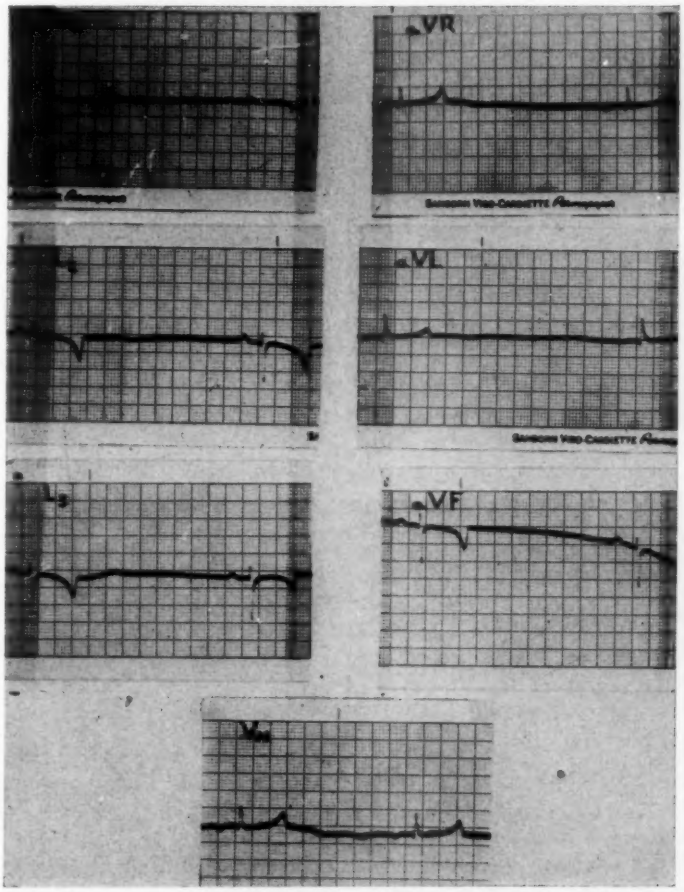

Fig. 1.—The three bipolar and the three augmented unipolar limb leads, and a unipolar chest lead (V_N). V_N was obtained in the base of the neck in the midline. Paper speed = 25 mm. per sec. Standardization 1 cm. = 1 mv.

INTERPRETATION OF THE ELECTROCARDIOGRAM

The negative P waves in aV_R, the diphasic, tiny P in aV_L, and the upright P in the aV_F, together with the upward ventricular complexes in aV_R and aV_L and downward QRS in aV_F indicate that the forelimbs face the atrial cavities

and the anterior epicardial ventricular surface. The unipolar lead aV_F apparently faces the posterior wall of the heart and/or the ventricular cavity. This electrical position is illustrated by the frontal projection of the mean vectors (Fig. 2) and corresponded well to the anatomic position found at autopsy (Fig. 3).

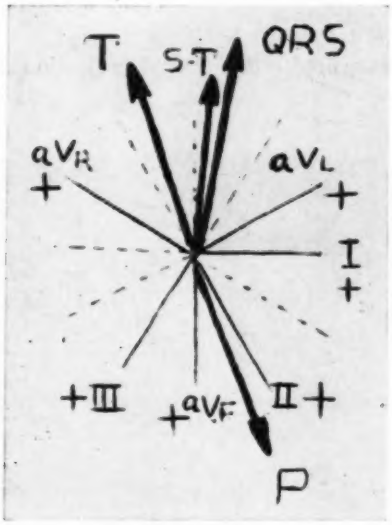

Fig. 2.—The frontal projection of the mean P, QRS, S-T, and T vectors.

Fig. 3.—The anatomic position of the heart during autopsy. The camel was lying on the back.

COMMENT

Fifty years ago it was stated that the larger the heart, the slower the heart rate.[3,4] This is true when comparing a mouse with an elephant, or a hamster with a whale,[2,5] but this relationship does not hold true among the large-sized animals. This becomes evident from the reports of White himself.[1,2] He found a rate of 30 per minute in the elephant's heart weighing about 20 kilograms, while the rate was 15 per minute in a beluga whale's heart that weighed 2.72 kilograms. The difference was explained by the factor of diving and the consequently increased vagal activity in the beluga whale. Our camel's heart weighed about a twentieth of that of the elephant (1.3 kilograms) and still the heart rate was about the same, or even less. Diving can certainly be excluded as a factor in our camel, and in the elephant as well. An additional noteworthy observation is that the duration of the various time intervals of the cardiac cycle in the camel is not much out of proportion to the slow heart rate as it has been found in the elephant. The width of the QRS complexes was identical with that of a man with much higher heart rate, and the Q-T interval corresponded to the predicted values determined by Bazett's formula.

After exercise there were no remarkable changes in heart rate, configuration, and time intervals of the electrocardiogram. The possibility exists that the effort was not sufficient to bring about hemodynamic changes which could be reflected in the electrocardiogram.

A more complete investigation of the cardiovascular system of the camel, with special emphasis on the cardiac and renal hemodynamics, is now being carried out in our laboratory.

SUMMARY

Electrocardiograms of a *Camelus dromedarius* were obtained at rest and after effort. The voltage of P-QRS-T was similar to that of the human electrocardiogram. The characteristic features were: bradycardia (26 per minute), normal width of QRS complexes, and prolonged P-R and Q-T intervals; the duration of these latter two intervals was proportional to the heart rate. The T waves were in the same direction as the QRS complexes, while the P waves were in the opposite direction. The electrical position of the heart, as obtained by the standard and unipolar limb leads, corresponded well to the anatomic position found at autopsy.

The technical assistance of Mr. Shmuel Werkson is gratefully acknowledged.

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Pericarditis and Myocarditis Caused by Toxoplasma: Report of a Case and Review of the Literature

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Toxoplasmosis is a protozoal disease which may be both congenital and acquired. Congenital toxoplasmosis was first diagnosed in 1937, by Wolf and Cowen,[1] who described an encephalomyelitis caused by Toxoplasma in a newborn baby. In this disease various grave lesions caused by encephalitis and chorioretinitis are encountered. Acquired toxoplasmosis was first described in 1940, by Pinkerton and Weinman.[2] The most usual symptoms of this disease are lymphadenitis, maculopapular exanthema, pneumonia, lesions of the liver, myositis, myocarditis, and encephalitis.[3] More attention has been paid to this disease since 1948, when the dye test and the complement fixation test were introduced.[4,5] By means of these serologic methods information on the frequency of occurrence of Toxoplasma antibodies was obtained.

Acquired toxoplasmosis is much rarer than congenital toxoplasmosis. Thalhammer[3] mentions in his monograph on toxoplasmosis that only 58 certain cases were reported up to June, 1956. New cases have since been recorded with increasing frequency. In the acquired form of the disease domestic animals are evidently the source of infection. Miller and Feldman[6] show that Toxoplasma antibodies are frequently found in domestic animals. The infection most probably takes place through the mouth or nose. This opinion is supported by the fact that infections have been observed in laboratory staff.

According to Thalhammer, the demonstration of Toxoplasma organisms by histologic examination or animal inoculation is necessary for the diagnosis of toxoplasmosis. The diagnosis is serologically certain only when rising or decreasing positive antibody titers, which indicate either active or vanishing infection, are found.

Myocarditis has been reported in 12 cases of acquired toxoplasmosis, according to Thalhammer. Six of these cases were diagnosed intra vitam. Paulley and associates[7] have further reported 5 cases in which the diagnosis was based upon an elevated antibody titer, which, however, was determined only once.

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Autopsy was made in 2 of these cases, but histologic examination revealed nothing indicative of toxoplasmosis. Thalhammer does not regard these cases as cases of myocarditis caused by Toxoplasma. Adamson and associates[8] also have described 3 cases of toxoplasmosis which showed electrocardiographic changes, but they mention no further details. Potts and Williams[9] reported a case of myocarditis in which the antibody titers were low despite an illness of 4 weeks' duration. Animal inoculation from autopsy material revealed Toxoplasma organisms. Thalhammer does not regard this case as one of myocarditis caused by Toxoplasma. In our opinion, however, this case must be considered as one of this disease. Only Guimaraes[10] has observed pericarditis, as well as myocarditis, caused by Toxoplasma. The diagnosis was made at autopsy. The previously described cases of myocarditis caused by Toxoplasma are collected in Table I.

TABLE I. THE CASES OF MYOCARDITIS IN ACQUIRED TOXOPLASMOSIS DESCRIBED IN THE LITERATURE

	MYOCARDITIS	ENCEPHALITIS	EXANTHEMA	PNEUMONIA	LYMPHADENITIS	MYALGIA	LESIONS OF THE LIVER	DIAGNOSIS	REMARKS
Pinkerton and Weinman[2] (1940)	+	+	+	+				*	
Pinkerton and Henderson[11] (1941) I	+	+	+	+			+	*	
Pinkerton and Henderson[11] (1941) II	+	+	+	+				*	
Guimaraes[10] (1943)	+	+		+				*	Also pericarditis
Prior and associates[12] (1953)	+	+			+			*	
Sexton and associates[13] (1953)	+	+	+	+		+		*	
Bengtsson[14] (1950) and Ström[15] (1951)	+	+	+	+	+			**	
Magnusson[16] (1951) I	+	+	+	+	+	+		**	
Magnusson[16] (1951) II	+	+	+		+	+		**	
Kass and associates[17] (1952)	+	+	+	+		+	+	**	Verified at autopsy
Pipkorn[18] (1953)	+							**	Also polyneuritis
Mohr[19] (1954)	+							**	
Potts and Williams[9] (1956)	+							**	Verified at autopsy

*Post-mortem.
**Intra vitam.

In myocarditis caused by Toxoplasma, focal infiltrates consisting of lymphocytes and plasma cells are found in the myocardium. These infiltrates often contain an abundance of eosinophils. Toxoplasma organisms are found in these lesions. Myocardial fibers show necrotic changes. It is interesting that the myocardium seems to be the place in which pseudocysts are often found after subclinical infection. These pseudocysts do not bring about electrocardiographic changes, as the experimental findings of Mohr and Hönig[20] show. These writers inoculated hamsters with Toxoplasma and found that the animals with electrocardiographic changes had a typical myocarditis caused by Toxoplasma, whereas those without electrocardiographic changes had Toxoplasma organisms in pseudocysts surrounded by intact myocardium.

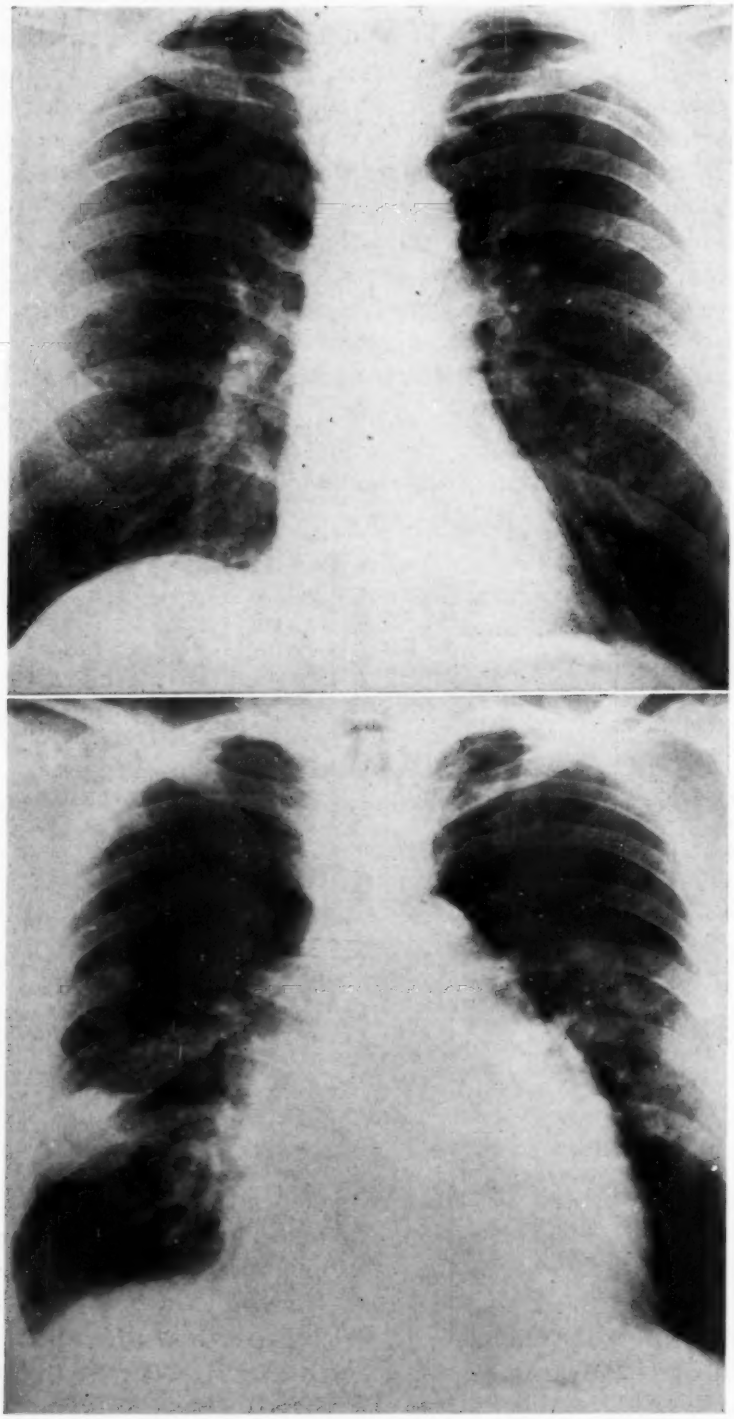

Fig. 1.—Serial roentgenographic findings. *A*, Feb. 2, 1957. Heart size is normal. *B*, June 12, 1957. Cardiopericardial shadow is considerably enlarged. Fluid accumulations appear in pleural sinuses and interlobar spaces. *C*, Nov. 7, 1957. The heart is still somewhat enlarged. The pleural effusion has disappeared. In all pictures healed tuberculous changes are seen.

As has been mentioned above, the diagnosis of myocarditis caused by Toxoplasma is rare, and only 1 case of pericarditis caused by Toxoplasma has been described. Following is the report of a case of myocarditis and pericarditis caused by Toxoplasma. The diagnosis was made during life.

CASE REPORT

A 54-year-old truck driver was admitted to the Third Medical Clinic, University of Helsinki, on June 10, 1957, because of dyspnea, fatigue, and dry cough. These symptoms had appeared a week before the admission.

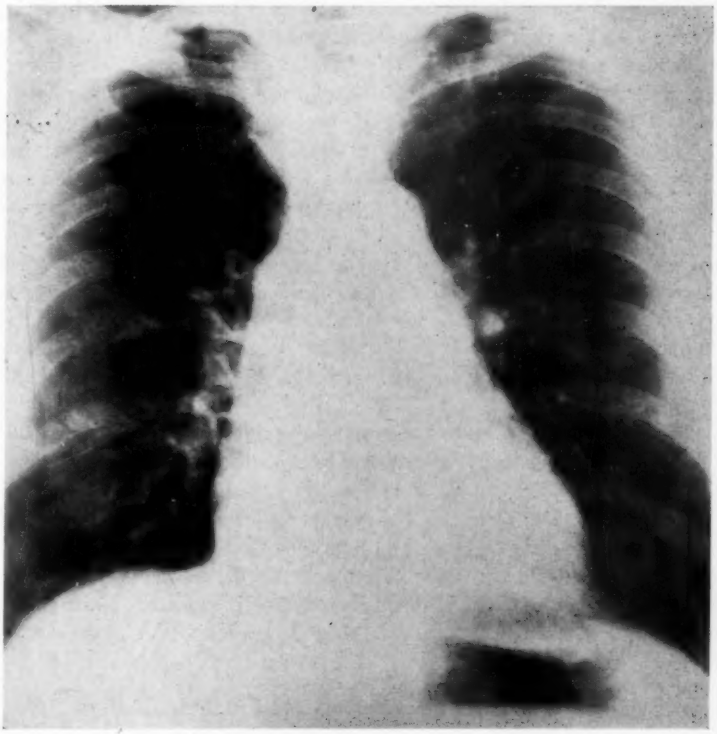

Fig. 1*C*.—*(For legend see opposite page.)*

In 1932, the patient had suffered an acute nephritis. In January, 1957, he began to feel tired and had headache, vertigo, nausea, and fever. His eyes were sensitive to light. He was admitted to the Aurora Hospital, where a slight stiffness of the neck and bilateral papillary edema were observed. Lumbar puncture revealed a pressure of 200 mm. Cerebrospinal fluid contained 132 cells per cubic millimeter, the majority of which were lymphocytes; its sugar content was 0.041 mg. per 100 ml., and the qualitative tests showed an increased protein content. Attempts to find tubercle bacilli by culture of sputum and by inoculation into guinea pigs gave negative results. Electroencephalography revealed changes indicating an organic brain lesion, but no definite focus of disturbances. The cell content of the cerebrospinal fluid rose to 447 cells per cubic millimeter, and decreased then to 10 cells per cubic millimeter. Leptospira antibodies could not be found in the serum. An attempt to cultivate poliomyelitis viruses from the stool gave negative results.

No cardiac murmurs were heard. The heart rhythm was regular. An electrocardiogram was not taken. X-ray examination (Fig. 1,*A*) revealed a normal heart. Healed tuberculous changes

were observed in both upper lung fields. The patient had fever for 1 week and was thereafter subfebrile for 2 weeks. He was given isoniazid, paraminosalicylic acid, and streptomycin, because a tuberculous etiology was suspected. His condition improved gradually and at the beginning of March, 1957, he left the hospital. Two months later he returned to his former occupation. He remained well until the beginning of June, when he began to suffer from dyspnea, dry cough, and fever.

On admission to the Third Medical Clinic, University of Helsinki, on June 10, 1957, the patient was seriously ill. His lips were cyanosed and he had severe dyspnea at rest. There was no icterus. Axillary temperature was 38.5°C. The pulse was irregular with a rate of about 90 beats per minute. The blood pressure was 140 mm. Hg systolic and 70 mm. Hg diastolic. A diffuse systolic lift was felt at the left border of the sternum. A rough pericardial friction sound was heard over the entire precordium. Analysis of the heart sounds was impossible because of this friction sound. Moist râles were heard over the posterior lower parts of both lungs, and there was a relative dullness on the right side. There was slight edema in both legs. An enlarged, but not tender, lymph node was felt in the right supraclavicular region. The liver and the spleen were not enlarged. Percussion revealed tenderness in the region above the right kidney.

Hemoglobin was 10.7 Gm. per 100 ml., and the white blood cell count was 7,400 per cubic millimeter. The erythrocyte sedimentation rate was 17. Serologic tests for syphilis were negative. The antistreptolysin titer was 40. There was a slight albuminuria. Microscopic examination of the urinary sediment revealed numerous erythrocytes and a few leukocytes and granulated casts.

The electrocardiogram revealed atrial fibrillation and a low voltage in all leads. The T wave was negative in Leads II, III, and aV_F, and biphasic in Leads aV_L, V_5, and V_6 (Fig. 2,*A*). X-ray examination revealed a definite enlargement of the heart. The pulmonary artery was prominent, and the peripheral vascularity of the lung fields was increased. Fluid accumulations were seen in pleural sinuses and interlobar spaces (Fig. 1,*B*). X-ray examination of the skull revealed nothing abnormal.

The Bromsulphalein excretion test showed a slight retention of the dye. The prothrombin content of the blood was decreased. Administration of vitamin K did not raise it. The albuminuria and hematuria observed on admission remained unchanged.

A determination of Toxoplasma antibodies was made. Both the dye test and the complement fixation test were strongly positive (Table II).

The enlarged lymph node in the right supraclavicular area was removed. An attempt was made to demonstrate Toxoplasma organism by inoculation into mice. This, however, gave negative results. Histologic examination of the lymph node revealed no changes indicating toxoplasmosis.

TABLE II. DATA ON TOXOPLASMA ANTIBODY TITERS

DATE	DYE TEST	COMPLEMENT FIXATION TEST
Aug. 21, 1957	1:1024	1:128
Sept. 5, 1957	1:16192	1:128
Oct. 1, 1957	1:65536	1:128
Oct. 8, 1957	1:65536	1:128
Oct. 24, 1957	1:262144	1:256
Nov. 6, 1957	1:262144	1:256
Nov. 21, 1957	1:65536	1:256

The patient was feverish for 1½ weeks. He developed an obstinate hiccough, and a maculopapular exanthema appeared. The pericardial friction sound disappeared gradually in 2 weeks. No cardiac murmurs could then be heard and the heart rhythm remained irregular. The first sound at the apex was accentuated. An x-ray examination made a week later showed that the size of the heart had decreased somewhat as compared with the earlier examination. The fluid

accumulation in the interlobar spaces of the right lung had increased. The temperature fell gradually to a normal level. The increased erythrocyte sedimentation rate returned to almost normal level. Simultaneously the T-wave changes in the electrocardiogram disappeared, whereas atrial fibrillation persisted (Fig. 2,*C*).

Because a tuberculous etiology had been suspected previously, a treatment with isoniazid, paraminosalicylic acid, and dihydrostreptomycin was started. After the diagnosis of toxoplasmosis had been made, the patient was given 6 Gm. of sulfafurazol and 25 mg. of Daraprim*, daily, for 2 weeks.

After 5 months of treatment at the hospital, the patient returned home in rather good condition. The atrial fibrillation still persisted. X-ray examination revealed that the heart was still somewhat enlarged. The pleural effusion had disappeared (Fig. 1,*C*). A month later the patient returned to the hospital for control examination. He stated that he had returned to his former occupation. He had no dyspnea. A physical examination revealed nothing abnormal, except a slight exanthema and irregularity in the heart rhythm.

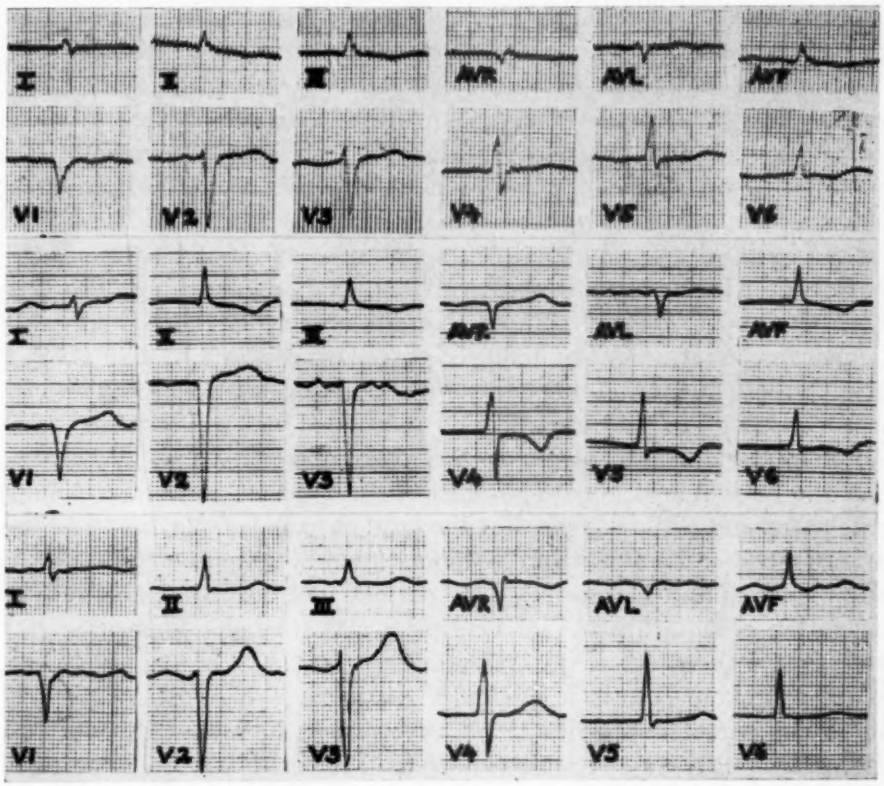

Fig. 2.—Serial electrocardiographic tracings of the case reported. *A*, June, 10, 1957. *B*, July, 15, 1957. *C*, Nov. 2, 1957.

Summary of the Case Report.—A case of pericarditis and myocarditis caused by Toxoplasma in a 54-year-old man has been reported. The patient had for some months a meningoencephalitis, probably of the same etiology. Besides pericarditis and myocarditis he had exanthema, lymphadenitis, and pleuritis. He also showed signs of lesions of the liver and the kidneys. During the disease the titers of Toxoplasma antibodies rose from 1:1024 to 1:262144 (dye test) and from 1:128 to 1:256 (complement fixation test). The patient was given both sulfafurazol and Daraprim for 2 weeks. After 5 months' stay at the hospital, he returned to his former occupation.

*Burroughs Wellcome & Company (U.S.A.), Inc., Tuckahoe, N.Y.

DISCUSSION

In our case the diagnosis of pericarditis caused by Toxoplasma was based upon clear pericardial friction sound, x-ray findings, and characteristic changes in the titers of Toxoplasma antibodies. Moreover, electrocardiographic changes suggested pericarditis. Only one case of pericarditis caused by Toxoplasma has been described in the literature.[10] In that case the diagnosis was made at autopsy. In addition to cellular infiltrations, Toxoplasma organisms were found in the pericardium. Earlier, seven cases of myocarditis in acquired toxoplasmosis were diagnosed during life. Six similar cases were diagnosed post mortem. In most of these cases lesions of other organs occurred also. In 2 cases, only myocarditis was observed.[9,19]

The prognosis of toxoplasmosis is considered to depend on the organs involved in the disease. The patients who had only lymphadenitis, pneumonia, or exanthema recovered, whereas 8 of 13 patients with myocarditis died.

The possible relapse in toxoplasmosis is not yet known for certain. The animal experiments of Frenkel[21] have shown that local relapse may be caused by rupture of pseudocysts. Since the patient had an earlier encephalitis (which may occur in toxoplasmosis), it is probable that this had also been caused by Toxoplasma, although the diagnosis was not made at that time.

On the basis of animal experiments the most effective treatment of Toxoplasma infection is the administration of both sulfonamides and Daraprim together. Eyles and Coleman[22] showed that these drugs have a synergistic effect. Experiences in the treatment of acquired toxoplasmosis in a human subject have been few. Wettingfield and associates[23] reported a case in which a severe toxoplasmosis caused by laboratory infection responded well to combined treatment with sulfonamides and Daraprim. In the case reported by Kass and associates,[17] in which the patient was given sulfadiazine for 2 weeks and chloroquine thereafter, the treatment could not prevent the fatal outcome of the disease. Similarly, the patient reported by Potts and Williams[9] died in spite of a week's treatment with sulfonamides and Daraprim. Our patient had begun to recover when the administration of sulfafurazol and Daraprim was started. It is difficult, therefore, to estimate the effect of the treatment.

Acquired toxoplasmosis is evidently no rarity. New cases are described with increasing frequency. Siim,[24,25,26] for instance, has reported over 100 cases from Denmark. Little attention has been paid to toxoplasmosis as an etiological factor in pericarditis and myocarditis. It seems possible, however, that pericarditis and myocarditis caused by Toxoplasma are not rare. It is important, therefore, to consider Toxoplasma as a possible etiological factor in cases of obscure pericarditis and myocarditis.

SUMMARY

The writers have described a case of pericarditis and myocarditis caused by Toxoplasma in a 54-year-old man, who recovered. The diagnosis of toxoplasmosis was based upon a strongly positive dye test and complement fixation test, which showed rising titers during the disease. The cases of pericarditis and myocarditis in acquired toxoplasmosis reported in the literature are reviewed.

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Incomplete Rupture of the Pulmonary Artery Based on Cystic Medionecrosis

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Relatively few cases of incomplete rupture of the pulmonary artery based on cystic medionecrosis have been reported. The reported cases appear to fall into two general categories: (1) those in association with pulmonary hypertension, and (2) those in association with Marfan's syndrome and other congenital anomalies.[1,2,7] In the former group, cases have been reported associated with mitral stenosis[3] and with patent ductus arteriosus.[4-6] In the latter group, it has been suggested that there may be some generalized malformation of connective tissues, including those of the pulmonary artery.[7] The purpose of this report is to present an additional case of cystic medionecrosis and incomplete rupture of the pulmonary artery, in this instance associated with so-called primary pulmonary hypertension.

CASE REPORT

G. T. (History No. B27014), a 47-year-old white woman, was first seen at the Johns Hopkins Hospital on Jan. 6, 1956, with a history of increasing exertional dyspnea since the summer of 1955. Discoloration of the feet had been noted in 1944; and in 1951, some swelling of the legs appeared. There was an episode of syncope after climbing a flight of stairs in the summer of 1955. Physical examination showed marked cyanosis of the legs, slight scleral icterus, marked distention of the neck veins, a blood pressure of 140/90 mm. Hg in the right arm, a Grade 2 apical systolic murmur, edema of the legs, and a slight amount of ascitic fluid. The right ventricle of the heart was markedly enlarged. The pulmonary conus was very prominent and the hilar vascular markings were increased. Cardiac catheterization showed no evidence of a shunt. Pressure in the right pulmonary artery was 128/52 mm. Hg. Diagnosis by Dr. Helen B. Taussig was primary pulmonary hypertension with right heart failure and cardiac cirrhosis. Subsequently, there was progressively increasing ascites, polycythemia, and cyanosis, and the patient expired evidently in right heart failure on Aug. 6, 1957.

Pathologic Examination.—With the exception of ascites and marked visceral congestion, the significant lesions were restricted to the heart, lungs, and liver.

Heart: The heart weighed 450 grams. The pulmonary conus, right ventricle, and right atrium with its tributary veins were all greatly dilated. The wall of the right ventricle measured 11 mm. in thickness. There was hypertrophy of its papillary muscles. Both the tricuspid and pulmonic valves were greatly stretched and appeared functionally incompetent. The remainder of the heart showed no significant lesions. The volume and thickness of the left atrium and ventricle were within normal limits.

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Study of the aorta with hematoxylin-eosin, toluidine blue, Gömöri elastic tissue stain, and periodic acid-Schiff reaction showed disintegration of the elastic tissue and accumulation of metachromatic material compatible with the age of the patient. No extensive pooling of metachromatic substance indicative of cystic medionecrosis was seen.

Pulmonary vessels: The main pulmonary trunk was greatly dilated, measuring 12 cm. in circumference. A few scattered, small atherosclerotic plaques were seen on the intimal surface. Two cm. above the pulmonic valve was a horizontal, irregular lesion having the appearance of an intimal tear, and involving almost the entire circumference of the pulmonary artery (Fig. 1). This appeared to have healed without deeper penetration of the wall. The two principal branches of the pulmonary artery were likewise greatly distended and contained atherosclerotic plaques.

Fig. 1.—Pulmonary conus and pulmonary artery. The right ventricle shows m rked hypertrophy and dilatation. The pulmonary artery is greatly dilated and an irregular intimal tear extends across it a short distance above the pulmonary valve.

This distention involved the branches of these vessels well into the lung substance, with marked atherosclerosis throughout. On microscopic examination the wall of the main pulmonary trunk showed marked cystic medionecrosis (Fig. 2) with extensive disruption of the elastic laminae and prominent increase in pooled metachromatic ground substance, as determined by staining with toluidine blue 1:1,000. A section taken through the area of the healed intimal tear showed loss of the normal structure of the intima and media, with loss of elastic fibers and replacement by collagenous scar (Fig. 3). No evidence of actual dissection was found. The small arteries of the lung showed, in some instances, structures having the appearance of organized, recanalized thrombi (Fig. 4), and, in other instances, evidence of marked arteriolar sclerosis (Fig. 5). The lungs themselves were of normal weight and presented no significant lesion other than the vascular changes.

Liver: The liver showed evidence of severe passive congestion and cardiac cirrhosis.

DISCUSSION

The close relationship between incomplete rupture of the aorta and dissecting aneurysm of the aorta has been well documented.[8-12] The close relationship of both these lesions to cystic medionecrosis is generally accepted. Like-

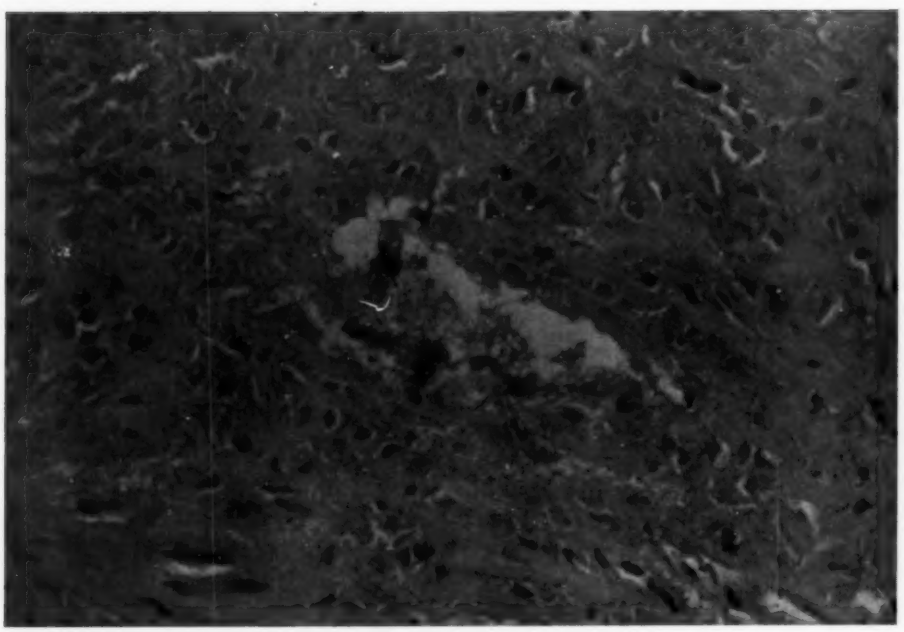

Fig. 2.—Wall of pulmonary artery adjacent to the tear showing prominent pooling of mucoid material. (Hematoxylin-eosin stain. Magnification, ×465; reduced ⅓.)

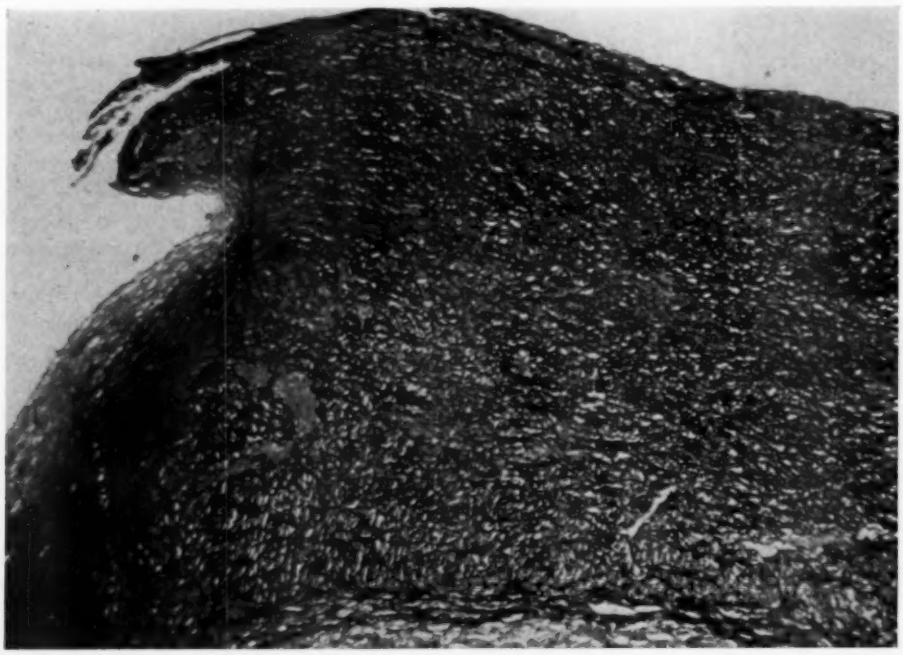

Fig. 3.—Area of tear in pulmonary artery showing interruption of intima and media. Elastic fibers (dark staining) are seen at right, but at left they end abruptly and are almost entirely replaced by collagen. (Gömöri elastic tissue stain. Magnification, ×80; reduced ⅓.)

Fig. 4.

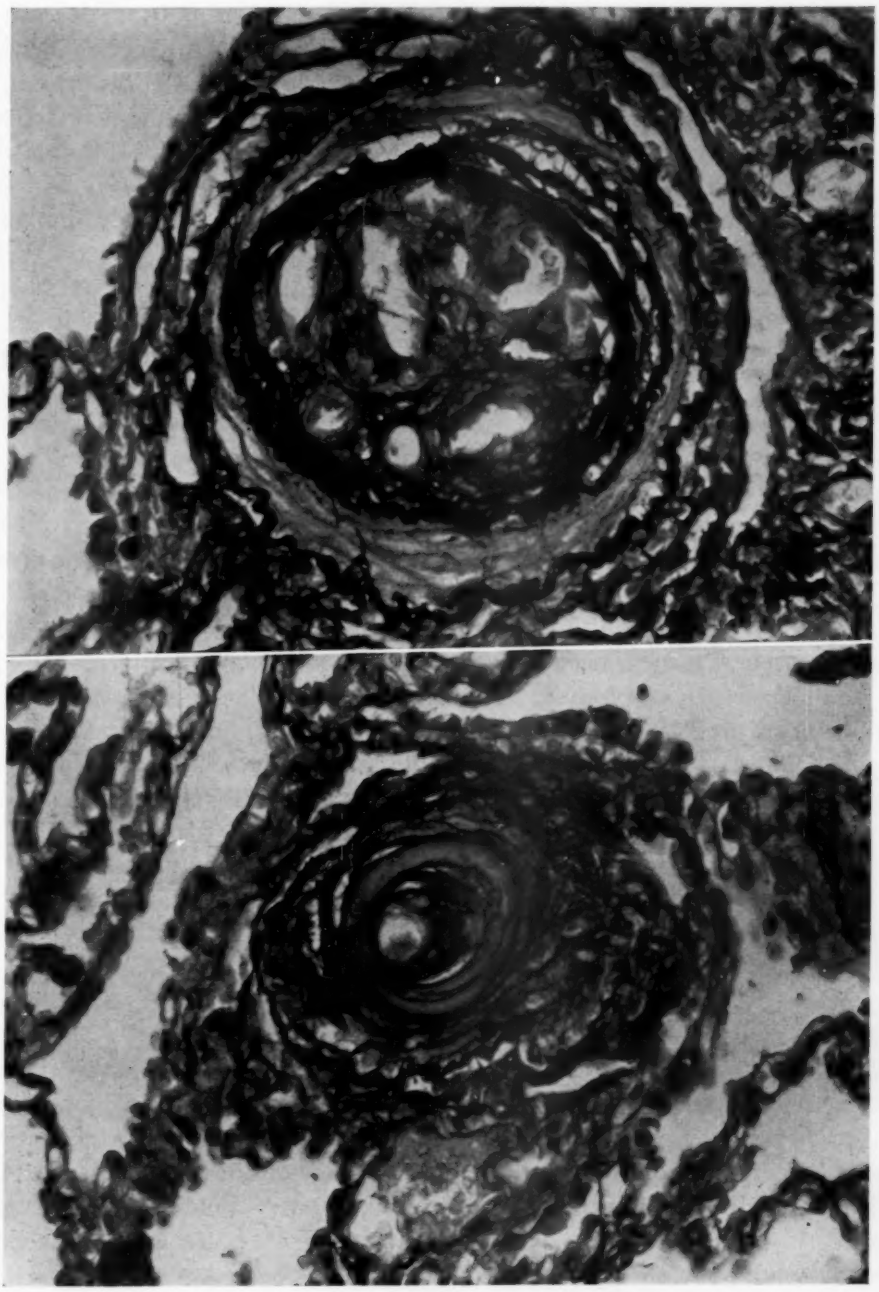

Fig. 5.

Fig. 4.—Small artery in lung showing splitting of elastic lamina and filling of lumen by recanalized thrombus. (Gömöri elastic tissue stain. Magnification, ×465; reduced ⅓.)

Fig. 5.—Small artery in lung showing marked splitting of elastic lamina with reduction in size of lumen by increased hyalinized intimal connective tissue ("arteriolar sclerosis"). (Gömöri elastic tissue stain. Magnification, ×465; reduced ⅓.)

wise there is abundant documentation of the close connection between systemic hypertension, on the one hand, and cystic medionecrosis and dissecting aneurysm of the aorta, on the other.[12,18-21]

The lesion in the present case appears to be an entirely analogous incomplete rupture occurring in the pulmonary artery.[13] The two features prominently associated with this lesion were cystic medionecrosis of the pulmonary artery and the presence of severe pulmonary hypertension. The pressures obtained in the pulmonary artery during cardiac catheterization approximated the levels normally found in the systemic circulation, a pressure of 5 to 6 times that which the pulmonary artery is equipped to tolerate.[22,28]

Cystic medionecrosis appears to be an exaggeration of the normal process of elastic fiber deterioration in large arteries. Taylor[14] has shown that in the newborn, metachromatic intercellular substance is evenly distributed through the entire width of the aortic wall, forming a delicate reticulated pattern between the elastic fibers. With advancing age, fragmentation of the elastic laminae occurs, with condensation of metachromatic material in these areas. This material appears to consist of chondroitin sulfate B and C.[15] In cystic medionecrosis there appears to be an increased degree of elastic fragmentation with pooling of extensive amounts of metachromatic material. The degree of cystic medionecrosis appears to be more marked in hypertensive than in nonhypertensive individuals of comparable age.[14]

It has been shown that elastic fibers break when they are stretched to 150 per cent of their original length, and that relatively little force is necessary to accomplish rupture.[16] This would seem to provide an explanation for the increased elastic fiber damage in both pulmonary and systemic hypertension. The accumulation of metachromatic mucopolysaccharide appears to represent a reaction of repair preceding collagen replacement of the damaged elastic fibers.[29]

Vital staining experiments with Evans blue in dogs suggests that the first portion of the pulmonary artery may be an area of special susceptibility to degenerative change.[17]

The factors which may cause tearing of the vessel wall in cases of cystic medionecrosis, with or without subsequent dissection, have been thoroughly reviewed by Gore.[12,18]

With regard to the actual cause of the pulmonary hypertension in the present case, the lesions found are of a nature similar to those in cases which have been described as primary pulmonary hypertension by some authors[22] and as recurrent thromboembolism by others.[23,24] The controversy hinges on whether the recanalized thrombi are embolic or are formed in situ. Some experimental work indicates that these may be embolic,[23,25,26] while other experimental evidence tends to support the theory of formation in situ.[27]

SUMMARY

A case of incomplete rupture of the pulmonary artery based on cystic medionecrosis is presented. This lesion was associated with so-called primary pulmonary hypertension. The effect of relative hypertension in elastic arteries is considered.

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Isolated Congenital Absence of the Right Pulmonary Artery: A Caution as to Its Diagnosis and a Proposal for Its Embryogenesis—Report of a Case With Review

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In 1952, at the time that Madoff, Strieder and Gaensler[1] reported the first clinically diagnosed case of absence of the right pulmonary artery, they were able to find, in a review that covered over a hundred years, only 9 previous recordings of congenital absence of one of the major branches of the pulmonary trunk. Four years later, in 1956, Emmanuel and Pattison[2] were to count a total of 46 such cases, most of which had been added because of newly refined angiocardiographic techniques. In the first review, almost all the cases had been verified at autopsy; in the second, the majority of cases had been diagnosed by angiocardiography, on the basis of a nonfilling branch of the pulmonary trunk. The disparity in these two figures, usually credited to the advance of diagnostic technology, is too vast to be explained so easily. Either the prosectors of the past have missed an obvious and apparently frequent anomaly, or—that which seems more warranted—current diagnostic criteria are inadequate and misleading.

The cases studied at autopsy characteristically have shown not only the absence of a pulmonary artery, but also the presence of an anomalous artery from the aorta or one of its branches to the affected lung. For this reason it seems essential to look for such an artery on the angiocardiogram and to doubt the diagnosis when it cannot be demonstrated. The simple filling defect seen at angiocardiography may have been—and has been[3,4]—caused by conditions other than a true congenital absence, e.g., atresia, severe stenosis, and thromboembolic obstruction.

The distinction is of interest not solely to the embryologist; for only in the case of true congenital absence of the pulmonary artery is the anomalous artery likely to be present, and this artery, on the one hand, may be of life-threatening importance by adding to the work load on the left side of the heart, or, on the other hand, may be of life-saving importance in the event that surgical removal of the unaffected lung is required.

Previous reviews have included cases both of absent right pulmonary artery and absent left pulmonary artery; cases in which the anomaly was only one of several major abnormalities of the heart and great vessels; and cases in which the defect appeared as an isolated phenomenon.

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TABLE I. PREVIOUSLY REPORTED CASES OF ISOLATED CONGENITAL ABSENCE OF A PULMONARY ARTERY

AUTHOR	ARTERY ABSENT	AGE	SEX	EVIDENCE FOR DIAGNOSIS	ARTERIAL SUPPLY TO AFFECTED LUNG
Ambrus[5] (1936)	Right	6 days	F	Autopsy	Branch of innominate
Miller[6] (1937)	Right	Newborn	M	Autopsy	Not stated
Findlay and Maier[7] (1951)	Right	4 mo.	F	Autopsy	Artery from left side of ascending aorta, coursing behind esophagus to enter right lung hilus
Madoff, et al.[1] (1952)	Right	14 yr.	F	Angiocardiography	(?) Branch from first portion of aortic arch
Steinberg, et al.[9] (1953)	Right	48 yr.	F	Angiocardiography	Not demonstrated
Flynn, et al.[11] (1954)	Right	25 yr.	M	Angiocardiography	Not demonstrated
Maier[8] (1954)	Right	9 yr.	M	Surgical exploration	4 mm. systemic artery from "high in the chest"
Maier[8] (1954)	Right	37 yr.	F	Angiocardiography	"Vessels which had filled from the aorta" (?) bronchial arteries
Wyman[10] (1954)	Left	15 yr.	F	Angiocardiography	Not demonstrated
Alexander, et al.[15] (1955)	Left	21 yr.	M	Angiocardiography	Not demonstrated
Overwater[17] (1957)	Right	11 yr.	F	Angiocardiography	(?) Dilated bronchial arteries

It might be profitable, however, in seeking the possible embryogenesis of this defect to single out those cases in which the abnormality existed only in its isolated form. In this respect it is of interest to note that absence of the left pulmonary artery and absence of the right pulmonary artery differ, in that absence of the left pulmonary artery most usually occurs along with other cardiac defects while absence of the right pulmonary artery most often occurs alone. Of the 23 cases of absent left pulmonary artery compiled in the latest review[2] 19 were in association with tetralogy of Fallot, with a higher than usual accompaniment of right-sided aortic arch, and 1 was associated with Eisenmenger's complex. Of the 21 reported cases of absent right pulmonary artery (19 recorded by Emmanuel and Pattison[2] and 2 published subsequently[16,17]) relatively few have been associated with other anomalies—principal associated anomalies being patent ductus arteriosus (4 cases[8,10,14]) and coarctation of the aorta (3 cases[8,10,13]).

A total of only 11 cases have been reported wherein the absent pulmonary artery was an isolated congenital anatomic defect. The findings in these cases are summarized in Table I. It is evident from a consideration of Table I that in more than half the cases reported as representing absence of a pulmonary artery, diagnosis was supported by angiocardiogram only, and in most of these the arterial supply to the affected lung was not demonstrated. These must be considered as the least positively established examples. In light of this, it is of interest that only the 2 reported cases of isolated absence of the left pulmonary artery fall into this category. The 9 remaining cases involved the right pulmonary artery.

In all but one of the autopsied cases (including the present one) an anomalous artery was found, and in the one exception[6] the arterial supply to the affected lung was not recorded. In the one case found at surgery[8] the anomalous artery was thought to be present; and in the original case diagnosed by angiocardiography by Madoff and his associates an anomalous arterial supply to the affected lung appeared to come from the first portion of the arch of the aorta.

It is the purpose of this paper to present a case of isolated congenital absence of the right pulmonary artery, to summarize briefly the aforementioned 11 cases, to illustrate the radiographic appearance which leads to diagnosis of this abnormality, and to propose a possible embryogenic cause for the defect.

CASE REPORT

A 6-week-old Negro boy was brought to the Boston City Hospital because of irritability and wheezing of 1 week's duration.

The boy was born after a full-term pregnancy, complicated only by "nausea throughout." No specific illnesses or trauma were noted, particularly within the first month of pregnancy (see under *Embryology*). Delivery was uncomplicated and the baby cried spontaneously. The birth weight was 7 pounds 14 ounces. On the fifth day the baby and mother were discharged, both in apparent good health. The baby continued to enjoy good health until 1 week prior to hospital admission, when he developed a "head cold." This was characterized by intermittent wheezing and excessive irritability and crying. There was no vomiting, diarrhea, fever, coughing, or rhinorrhea. Cyanosis was thought to be present in the lips and extremities with vigorous crying.

Review of systems was negative. Family history revealed no illnesses other than rheumatic heart disease in the maternal grandmother.

Physical examination showed a well-developed, well-nourished Negro infant who was breathing rapidly, crying, and retracting slightly at the sternum. He weighed 4.5 kilograms and mea-

ured 56 cm. in length. The head and chest circumferences were equal at 38 cm. These measurements put him in about the twenty-fifth percentile for his age. Temperature was 99.2°F. rectally; pulse, 160 per minute and regular; respirations, 80 per minute; and blood pressure, 90/68 mm. Hg. No cyanosis was noted on examination. There was distention of neck veins while the infant was held sitting and not crying. The chest was symmetrical, retracting slightly, with no râles or rhonchi noted on either side. The heart was slightly enlarged 1 cm. beyond the mid-clavicular line. A Grade 1 soft systolic murmur was heard at the left parasternal area in the fourth intercostal space. The pulmonic second sound was split and louder than the aortic second sound. A gallop rhythm was occasionally noted. The liver was felt 3 cm. below the costal margin. The spleen was not felt, and there were no masses in the abdomen. Neurological examination was unremarkable.

Routine examination of blood and urine was not remarkable. Cultures of nose and throat grew normal flora; cultures of the blood were negative. Chest x-ray (Fig. 3) showed a heart that was enlarged and round in shape. The right side of the chest was considerably more radiolucent than the left, and there was the appearance of diminished vascularity in the right lung. The lungs were otherwise unremarkable. The electrocardiogram showed only right ventricular enlargement.

In the hospital the baby was started on Digoxin, 0.125 mg. intramuscularly every 8 hours for 4 injections, and then given the first of a planned daily oral dosage of 0.1 mg. Digoxin. On the third hospital day the baby suddenly stopped breathing during a change of diapers, and died. His clinical diagnosis was congenital heart disease of undetermined type.

Autopsy Report.—At autopsy the body weighed 4.1 kilograms and measured 55 cm. in length, was fairly well developed for its age. Cyanosis or lividity was visible on the lips and fingernail beds, although it was difficult to distinguish because of the dark negroid skin.

Remarkable findings were as follows: The heart was normally formed, large, globular in shape, with prominent right ventricular hypertrophy. There were no lesions of the myocardium or endocardium. Measurements of the thickness of the ventricular walls made at the base of the papillary muscles showed the right ventricle to be 0.7 cm. and the left ventricle 0.4 cm. The aorta and pulmonary trunk both arose from their appropriate chambers with no overriding. The pulmonary valve measured 3.5 cm. in circumference, and the aortic valve, 2.5 cm. The tricuspid and mitral valve circumferences were 4.8 and 5.0 cm., respectively. All the valves were well formed and contained the normal number of leaflets. There was no septal defect, the only communication between the left and right side of the heart being an anatomically patent foramen ovale which measured 0.4 cm. in diameter. Both coronary arteries arose from the aorta, and their distribution was normal.

The following situation was found in the major vessels leaving the heart (Figs. 1 and 2): (1) The pulmonary trunk led to the left lung alone and gave no branch to the right lung. The entire wall, from intima to adventitia, was smooth and uninterrupted. No dimpling or other suggestion of an abortive or atretic right pulmonary artery could be seen. (2) An anomalous artery arose from the ascending aorta just proximal to the innominate artery and entered the hilus of the right lung. The circumference of this anomalous artery was 0.2 cm. In circumference the aorta measured 1.0 cm. at point of communication with the ductus arteriosus and 1.7 cm. in its descending portion. The pulmonary trunk measured 1.0 cm. in circumference. The ductus arteriosus was still patent and its wall thickened. External circumference measured 0.6 cm. and internal circumference, 0.2 cm. The total heart-lung-trachea block weighed 160 grams, or about 50 grams more than the expected weight at this age.

The lungs showed congestion and edema similarly on both sides. The gastrointestinal tract showed some patchy congestion of blood vessels. The liver was congested and weighed 175 grams, with an expected weight at this age being 123 grams. All other organ systems, including the brain, were normal and no other congenital anomalies were noted.

Microscopic examinations of all organs confirmed the above findings. Sections of both lungs were stained with hematoxylin and eosin, Verhoeff's elastic tissue stain, periodic acid-Schiff stain, silver stain for reticulum, and phloxine-methylene blue. These showed congestion and edema. In the left lung sections emphysema alternating with atelectasis was marked. In the right lung there was congestion of the alveolar capillaries, with bulging of the vessels into the alveolar sacs. Occasional arterioles showing intimal proliferation were present.

Fig. 1.

Fig. 2.

Fig. 1.—Isolated congenital absence of the right pulmonary artery. The heart-lung block shows the pulmonary trunk going to the left lung only, and prominent right ventricular enlargement of the heart.

Fig. 2.—Anomalous right pulmonary artery. The probe isolates the artery arising from the ascending aorta proximal to the great vessels and entering the hilus of the right lung.

DISCUSSION

Radiography.—The routine posteroanterior chest x-ray of this patient (Fig. 3), taken on admission, is somewhat typical of those seen in the past with this abnormality. Often it is the first unusual finding. Remarkable in the adult cases reported was the paucity of complaints—the usual complaints being cough, recurrent pneumonia, hemoptysis, and diminished exercise tolerance, but rarely anything of limiting severity. Infant cases—the only ones seen so far at autopsy—died after severe dyspnea and cyanosis.

Fig. 3.—Posteroanterior x-ray of the chest. The heart is enlarged and rounded in shape. There is increased radiolucency of the entire right lung. Rotation of the patient is present, but there is probably shifting of the heart to the right.

The heart may be enlarged, as in this case, or not. (Some rotation of the patient was present at time of exposure.) Four signs, however, should lead to the suspicion of such a diagnosis. Three have recurred so invariably as to be almost cardinal[1,8-11,15] and the fourth if present is considered pathognomonic. These signs are: (1) increased radiolucency of the affected lung, usually interpreted as diminished pulmonary vascular markings; (2) diminished size of the affected hemithorax with (3) mediastinal shift and occasionally actual herniation of the opposite lung; and (4) absent "hilar comma" shadow. This last finding was described by Danelius[18] as being pathognomonic of such conditions, for the reason that the shadow represents the descending main branch of the pulmonary

artery. In these cases, however, it has been detected infrequently on routine films because of the mediastinal distortion and obscuration by the cardiac shadow.

The clinical diagnosis of this condition is best made by angiocardiography. It is important to emphasize, however, that demonstration must be made not only of a nonfilling pulmonary artery but, in addition, if possible, of a *filling* anomalous systemic artery. Otherwise the actual situation may be one of a pulmonary artery not absent, but, rather, obstructed in some manner. In the latter case, blood supply to the affected lung would go by way of dilated bronchial arteries.

Should an emergency arise requiring resection of the unaffected lung and were the anomalous artery truly present, one could hope to anastomose the proximal end of this artery to the pulmonary trunk and thus supply the remaining lung with unoxygenated blood from the right side of the heart.

Embryology.—Most investigators of this condition agree that congenital absence of a pulmonary artery involves some defect in the development of the sixth aortic arch. This is a paired arch which forms by a fusion of branches leaving either side of the aortic sac to branches arising from the two dorsal aortae. On each arch a bud develops where the two branches fuse, separating the proximal from the distal portion of the arch. Ultimately the pulmonary artery on each side is made up of components of the proximal portion of the arch plus the bud. The distal portions of the sixth arch have different fates. That on the right disappears, while that on the left persists beyond birth as the ductus arteriosus.

Simultaneously the aortic sac itself undergoes change, differentiating further into the primitive cardiac bulb and the truncus. With this differentiation the truncus becomes the primordial point of attachment for the sixth arch vessels. Bremer[19] and Congdon[20] have given excellent descriptions of the above, and they, and particularly Llorca,[21] have pointed out an additional phenomenon. The right sixth arch, while it is developing, migrates dorsally across the truncus until it meets the left sixth arch, where both then arise from a common trunk on the left side of the truncus. While this migration takes place, the aortopulmonary septum divides the truncus into two channels, the aorta and the pulmonary trunk (Fig. 4). Division of the truncus is complete between the thirty-first and thirty-sixth day, and is apparent in the 4-mm. and 6-mm. embryos.[20]

The exact nature of the defect in embryogenesis which produces isolated absence of a pulmonary artery has never been ascertained. The causes, in fact, could be many. Most authors have felt that it is a result of failure of development or early obliteration, due to mechanical factors of one side of the sixth aortic arch. However, no satisfactory accounting has been given for the anomalous artery, which in almost every well-established case has arisen from the aorta proximal to the innominate artery. Even Ambrus,[5] although he lists the anomalous artery as arising from the innominate, accompanies his report with an illustration showing a common origin from the aorta of both anomalous artery and innominate artery with an immediate separation of the two vessels. This appears to represent instead a merging of two closely placed arteries.

Maier[8] felt the anomalous artery to be a result of persisting communications between dorsal aorta and pulmonary plexus, communications which in the nor-

mally developing embryo are only temporary in duration. Since these communications appear in the embryo distal to the sixth arch, in relation to the cardiac bulb, it seems unlikely that they could give rise to an artery which arises from the ascending part of the aorta, proximal even to the great vessels of the arch, derivatives in part of the third and fourth aortic arches.

Another explanation, that of Ambrus,[5] accounts for the anomalous artery on the basis of an abnormally persisting right fifth aortic arch. He postulates further that the right fifth arch sends a dorsal bud to the lung. The end result, an artery entering precisely at the hilum, requires in all the concurrence of not one, nor two, but three unlikely phenomena.

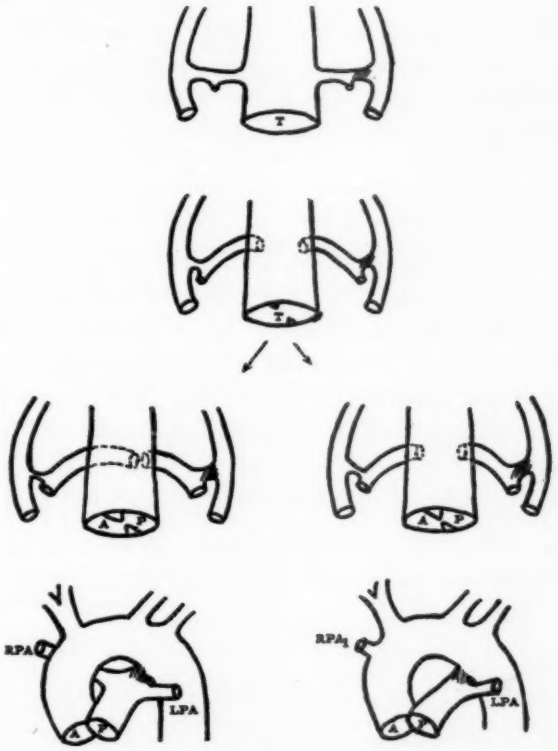

Fig. 4.—(Adapted from Collett and Edwards,[22] with the authors' permission.) Diagram of the development of the sixth aortic arch and the truncus arteriosus. The normal development (left) shows migration of the right sixth aortic arch to the left side of the truncus as the latter is divided by the aortopulmonary septum. Final result is a pulmonary trunk with main branches to the right and left lungs. Defective development (right) shows failure of migration to keep pace with division of the truncus. The final result is a pulmonary trunk with a single branch to the left lung and anomalous origin of the right pulmonary artery. Shaded portion represents ductus arteriosus.

An explanation that seems more probable, in that it is simpler, is that the defect is not one of failure of development of the right sixth aortic arch but, rather, of misplaced attachment. It is possible that during the migration phase of the right sixth arch and the simultaneous division of the truncus, the former is retarded sufficiently so that when the truncus splits, the right sixth arch is caught on the wrong side (Fig. 4). Thus, the anomalous artery arising from the aorta is right pulmonary artery in ambition only; its name, commensurate with its

paternity, deserves to be that of anomalous right pulmonary artery. The defect then, although it cannot be pinpointed as to first cause, can be located somewhat as to time. It should be detectable in the embryo just prior to, or at the time of, the division of the truncus, i.e., about the thirty-first to thirty-sixth day.

That the aorta and pulmonary trunk each arose without abnormality from the heart, and that no abnormal septal defect was present in the heart itself, are both indicative of a normally developing aortopulmonary septum in the case presented. It is not likely, therefore, that the absent right pulmonary artery was secondary to some abnormality here. The same cannot be said for those cases of tetralogy of Fallot and Eisenmenger's complex, in which the alteration seems to have taken place in the formation of the aortopulmonary septum, producing overriding of the aorta, disparity in the calibers of the aorta and pulmonary artery, and septal defects. The absence of pulmonary arteries in these cases are most probably phenomena consequent to the abnormal division of the truncus, which affects, in addition, the other paired vessels.

SUMMARY

A case of isolated congenital absence of the right pulmonary artery, diagnosed at autopsy, is presented, and 11 previously reported cases are briefly reviewed. In this case an anomalous artery from the ascending aorta to the hilus of the right lung, believed to be an anomalous right pulmonary artery, was found, and the significance of the presence of this artery is emphasized.

Radiographic appearance and angiocardiographic demonstration of this condition is discussed.

A possible embryogenic mechanism for this defect is suggested.

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The Effect of Theophylline Ethylenediamine on the Pulmonary Circulation

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Theophylline ethylenediamine (TED) has a widespread action on circulation and ventilation. It increases the cardiac output,[1-7] increases the heart rate,[2,4] either lowers the systemic blood pressure slightly[1,3] or raises it slightly,[2,5,7] lowers the pressure in the right atrium[3,6] and pulmonary artery,[1-4,7a] lowers the pulmonary capillary venous pressure (PCV),[1,4] and lowers the resistance both in the systemic[1-3,7] and pulmonary circulations,[1,3,7a] more in the latter. TED increases the minute ventilation[2,4,7] and abolishes Cheyne-Stokes respiration.[8] Furthermore, it has a diuretic action,[2,5] and is claimed to have a dilating effect on coronary arteries.[9]

This study was undertaken to determine the action of TED on pulmonary circulation and ventilation, with the possibility in mind that there might be a connection between these actions, inasmuch as it has been maintained that improvement in pulmonary ventilation will also improve the circulation through the pulmonary vascular bed.[10]

MATERIAL AND METHODS

Twenty-one patients with various heart and lung diseases have been examined. The age and diagnosis of the patients are shown in Table I, together with their physical characteristics.

Ventilatory studies with TED were carried out the day before the catheterization procedure. A spirogram was registered on the moving drum of a Krogh spirometer, and maximal breathing capacity was measured with collection of the expired air in a Douglas bag. TED 0.30 Gm. dissolved in 10 c.c. physiologic saline solution was given slowly intravenously in the course of 5 minutes. Ten minutes afterward ventilatory measurements were repeated.

The patients were sedated with a barbiturate (ally-propynal) 0.10 Gm. on the evening before, and 0.10 Gm. on the morning of, the catheterization procedure. They were given a light breakfast and came to the laboratory at 1 P.M. Right heart catheterization was carried out in the usual way. About 10 minutes after introduction of the catheter into the pulmonary artery, measurements of pulmonary artery and PCV pressures were carried out, the pressures being registered on an Elmquist 4-channel electrocardiograph with the aid of a Tybjaerg Hansen manometer[11] registering undamped and critically damped pressures. The reference level for the pressure measurements was the fourth intercostal space in the anterior axillary line. Brachial artery pressure was measured by cuff, the mean pressure being calculated as diastolic plus one-third pulse pressure. A Cournand needle was placed in the femoral artery, and cardiac output was estimated using the Fick principle. Expired air was collected in a Douglas bag for 3 minutes

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and analyzed for O_2 and CO_2 content by a Haldane apparatus. Blood analysis was done with the manometric van Slyke apparatus. Arterial pH was measured with the glass electrode (Radiometer, Copenhagen), and arterial pCO_2 was calculated from pH and CO_2 content, using the nomogram of Singer and Hastings.[12]

TED 0.30 Gm. was then given slowly intravenously, as in the ventilatory studies. Pressures in the pulmonary and brachial arteries were measured every 5 minutes for 25 minutes. After 10 minutes, PCV pressure was again measured, and from 12 to 15 minutes after the injection of TED, a repeat cardiac output determination was done.

The following formulas have been used in calculation:

$$\text{Peripheral arterial resistance} = \frac{\text{Brachial artery mean pressure} \times 1{,}332 \text{ dynes-sec.-cm.}^{-5}}{\text{Blood flow per second}}$$

$$\text{Pulmonary arteriolar resistance} = \frac{\text{Pulm. art. mean} - \text{PCV pressure} \times 1{,}332 \text{ dynes-sec.-cm.}^{-5}}{\text{Blood flow per second}}$$

$$\text{Work of the right ventricle} = \frac{\text{Pulm. art. mean press.} \times \text{Blood flow per min.} \times 13.6 \text{ Kg. meter per minute}}{1{,}000}$$

In Table II $\bar{x}$ and $\bar{y}$ denote the arithmetic mean of the observed values before and after TED, while $\bar{z}$ denotes the difference between $\bar{x}$ and $\bar{y}$.

The effect of TED has been tested by means of Student's t-test,[13] where $t = \frac{\bar{z} \cdot \sqrt{n-1}}{s_z}$ follows the t-distribution with $n - 1$ degrees of freedom, and where s is the standard deviation of $\bar{z}$.

The correlation coefficient has been calculated from the formula $r = \frac{\Sigma_{xy}}{\Sigma_x^2 \cdot \Sigma_y^2}$, where Σ_{xy} is the sum of the products of the deviate values of x and y, and Σ_x^2 and Σ_y^2 are the sums of the squares of these deviate values.

TABLE I. MATERIAL FOR STUDY OF THE EFFECT OF THEOPHYLLINE ETHYLENEDIAMINE ON THE PULMONARY CIRCULATION

NUMBER	NAME	SEX	AGE	DIAGNOSIS	HEIGHT (CM.)	WEIGHT (KG.)	BODY SURFACE AREA
1.	N.J.	F	74	Arteriosclerotic heart disease	168	58.2	1.68
2.	J.B.	M	58	Mitral stenosis	172	71	1.84
3.	H.H.	M	59	Heart disease of unknown origin	172.5	77	1.90
4.	F.L.	M	61	Arteriosclerotic heart disease	169	74	1.85
5.	M.S.	F	51	Mitral stenosis	163.5	67.5	1.74
6.	K.H.	F	55	Mitral stenosis	166	55.5	1.61
7.	S.L.	F	68	Myocarditis	160.5	49	1.50
8.	B.A.	M	42	Cardiac amyloidosis	169	64	1.74
9.	P.W.	M	43	Mitral stenosis	172	67	1.80
10.	M.L.	F	16	Mitral stenosis	167	62.6	1.70
11.	K.P.	M	72	Arteriosclerotic heart disease	152	53.7	1.50
12.	R.S.	M	67	Anomalous pulmonary veins	177	66.5	1.82
13.	M.K.	M	66	Aortic stenosis	178	73.5	1.92
14.	A.H.	F	40	Mitral stenosis (operated)	160	50.5	1.50
15.	E.S.	F	51	Mitral stenosis*	159	62.1	1.64
16.	O.H.	M	53	Mitral and aortic stenosis and pulmonary emphysema	171	52.5	1.60
17.	E.P.	F	74	Boeck's sarcoid	151.5	58.5	1.55
18.	A.B.	F	39	Bronchial asthma	162	56.7	1.60
19.	N.S.	M	59	Bronchial asthma	164	59.7	1.65
20.	A.B.	F	49	Bronchial asthma	151	36.5	1.25
21.	E.M.	F	51	Cor pulmonale	152	54.5	1.50

*This patient had clinical evidence of mitral stenosis, but the PCV pressure did not confirm the clinical impression.

RESULTS

The effect of 0.30 Gm. TED on heart rate, blood pressure, pulmonary artery pressure, PCV pressure, cardiac output (calculated as cardiac index), peripheral arterial and pulmonary arteriolar resistances, work of the right ventricle, arterial O_2 saturation, arterial pCO_2, tidal air, vital capacity, and maximal breathing capacity is shown in Table II.

The table shows a significant fall in blood pressure, pulmonary artery pressure, peripheral arterial and pulmonary arteriolar resistances, work of the right ventricle, and pCO_2, while there is a significant rise in heart rate and maximal breathing capacity. The changes in PCV pressure, cardiac index, arterial O_2 saturation, tidal air, and vital capacity are statistically not significant.

The ventilatory improvement gave no change in arterial O_2 saturation, while there was a significant fall in arterial pCO_2. This fall in pCO_2 following TED has been observed previously by Wechsler, Kleiss and Kety[14] and by Galdston and Geller.[15] The arterial O_2 saturation in 9 of 10 patients with mitral stenosis observed by Dulfano and co-workers[1] showed an increase as it did in 4 patients with pulmonary emphysema studied by Galdston and Geller.[15]

The significant increase in heart rate in our patients is in accord with the findings of Fowell and co-workers,[2] and of Werkø and Lagerløf,[4] while Starr and his associates[7] found a slight decrease of 1.7 per cent. This increase in heart rate is due to a stimulting effect of TED on the heart.[16]

There was a significant fall in systemic blood pressure and a more pronounced fall in pulmonary artery pressure, while the fall in PCV pressure was not significant. There was a slight increase in cardiac index, but the increase was statistically not significant. With the formula for vascular resistance in mind ($\text{resistance} = \frac{\text{pressure gradient}}{\text{blood flow}}$), it is to be expected that the fall in both peripheral arterial resistance and pulmonary arteriolar resistance would be statistically significant. That the fall in the latter is not more pronounced on statistical evaluation is due to the great spread of the observed values for pulmonary arteriolar resistance, from 67 to 751 dynes-sec.-cm.$^{-5}$.

DISCUSSION

TED improved the lung ventilation in these patients with various heart and lung diseases when it was measured as maximal breathing capacity, while there was no significant change in tidal air and vital capacity. Improvement in lung ventilation after TED has been observed by Starr and associates,[7] by Fowell and co-workers,[2] and by Werkø and Lagerløf,[4] who found an increase in minute volume of ventilation after TED. As in our cases, Werkø and Lagerløf found no change in vital capacity in their hypertensive patients. The improvement in maximal breathing capacity in our patients indicates an improvement in the mechanics of breathing and is probably due to a bronchodilating effect of TED.

The effects of TED on the systemic circulation observed in this series are similar to the results of Werkø and Lagerløf and of Dulfano and co-workers.[1]

A rise in cardiac output was noted in a large number of reports,[2,3,5-7] and a fall in peripheral arterial resistance was noted in those cases in which it was calculated.[1-4,7] The reaction of the systemic blood pressure to TED is somewhat different in various reports, there being either a slight fall as in our cases[1,3] or a slight rise.[2,5,7] This difference in reaction does not seem to be related to the dose of the drug or to the type of patients studied, but to the site of the most pronounced effect of TED; a direct action on the systemic blood vessels gives a fall in blood pressure, while an action on the medullary vasomotor center will produce a contraction of the blood vessels with a rise in blood pressure.[16] One of our patients showed a severe drop in blood pressure after 5 minutes. Fig. 1 shows that this pressure fall was accompanied by a fall in heart rate, but not in pulmonary artery pressure. It is known that TED may produce syncope and even death in patients with cardiovascular disease. Our observation, like that of Condorelli[17] suggests that this is due to a severe peripheral vasodepression, like that seen in "vasogenic" shock and in shock due to spinal anesthesia.

TABLE II. THE EFFECT OF THEOPHYLLINE ETHYLENEDIAMINE ON CIRCULATION AND VENTILATION IN 21 PATIENTS WITH HEART AND LUNG DISEASES

NO.	NAME	BLOOD PRESSURE MEAN (MM. Hg)		HEART RATE		PULM. ART. MEAN PRESSURE (MM. Hg)		PCV MEAN PRESSURE (MM. Hg)		CARDIAC INDEX (L./MIN./M.^{2})		PERIPH. RESIST. (DYNES-SEC.-CM.$^{-5}$)	
		B	A	B	A	B	A	B	A	B	A	B	A
1	N.J.	123	113	75	94	14	9	4	3	1.7	1.8	3,440	3,000
2	J.B.	140	135	76	65	35	30	17	19	1.4	1.5	4,350	3,910
3	H.H.	112	112	90	80	8	5	0	−1.5	2.6	2.4	1,810	1,960
4	F.L.	103	98	90	95	11	6	2.5	1	4.0	3.2	1,110	1,320
5	M.S.	110	108	72	76	25.5	19.5	10	12.5	2.1	2.7	2,400	1,840
6	K.H.	97	98	84	100	11	7.5	5.5	4	2.5	2.6	1,930	1,870
7	S.L.	85	85	92	108	10	6	4.5	2.5	1.5	1.8	3,020	2,520
8	B.A.	92	90	100	112	28	24	18.5	21	1.6	1.6	2,820	2,580
9	P.W.	98	90	76	72	26.5	25.5	20	16	2.9	3.3	1,500	1,210
10	M.L.	117	115	90	114	15.5	8	4.5	4.5	4.2	4.7	1,310	1,150
11	K.P.	90	90	100	100	38	13	7	6	2.2	2.1	2,180	2,280
12	R.S.	103	98	96	100	8	6	0.5	−0.5	—	—	—	—
13	M.K.	75	82	110	112	28	21.5	19	16.5	3.0	2.2	1,050	1,550
14	A.H.	88	87	52	54	45.5	37	—	—	1.6	1.8	2,930	2,580
15	E.S.	108	108	114	128	26	21	2.5	2.5	2.9	2.8	1,820	1,880
16	O.H.	102	97	104	112	37.5	29.5	—	—	2.8	2.8	1,820	1,760
17	E.P.	102	85	60	64	8	6	2.5	2.0	2.3	2.1	2,290	2,090
18	A.B.	88	82	96	112	11	5.5	0.5	0	2.9	2.8	1,520	1,460
19	M.S.	95	92	80	84	8	6.5	−0.5	−0.5	6.2	8.1	740	550
20	A.B.	98	98	104	112	9	6	2.5	−2.5	4.2	5.2	1,490	1,260
21	E.M.	100	100	120	140	70	58	7	—	2.3	2.3	2,320	2,320
		$\bar{x}$ = 101.2 $\bar{y}$ = 98.2 $\bar{z}$ = 3.0 t = 2.829		$\bar{x}$ = 89.6 $\bar{y}$ = 96.9 $\bar{z}$ = −7.3 t = 3.527		$\bar{x}$ = 22.6 $\bar{y}$ = 16.7 $\bar{z}$ = 5.9 t = 5.248		$\bar{x}$ = 6.76 $\bar{y}$ = 5.88 $\bar{z}$ = 0.88 t = 1.805		$\bar{x}$ = 2.745 $\bar{y}$ = 2.890 $\bar{z}$ = −0.145 t = 1.107		$\bar{x}$ = 2,112 $\bar{y}$ = 1,855 $\bar{z}$ = 257 t = 5.395	
		0.02>P>0.01[x]		0.01>P>0.001[xx]		P<0.001[xxx]		0.10>P>0.05		0.30>P>0.20		P<0.001[xxx]	

B and A = before and after theophylline ethylenediamine.

The most pronounced effect of TED in our patients was on the pulmonary circulation, where a fall in pulmonary artery pressure and pulmonary arteriolar resistance was observed. In considering a fall in pressure in the pulmonary circulation there are several factors to be taken into account, and the conclusion that the agent under investigation must have a direct dilating effect on the pulmonary blood vessels is not justified without considering these factors.

Some of the factors to be considered are discussed below:

1. *Effect of Changes in Systemic Blood Flow on the Pulmonary Circulation.*—Changes in output of the right ventricle will easily influence the pressure in the pulmonary circulation. An example of this influence is the action of hexamethonium bromide, which, like tetraethylammonium chloride,[18] produces a dilatation of systemic blood vessels with pooling of blood in this part of the circulation, reduction of the venous return, and a parallel fall in pulmonary artery and PCV pressures.[19] Increase in blood flow will increase the pressure in the pulmonary artery when there is a restriction to blood flow either from a stenotic mitral valve or from vascular narrowing in the lungs.

TABLE II. THE EFFECT OF THEOPHYLLINE ETHYLENEDIAMINE ON CIRCULATION AND VENTILATION IN 21 PATIENTS WITH HEART AND LUNG DISEASES—CONT'D

PULM. ART. RESIST. (DYNES-SEC.-CM.$^{-5}$)		WORK OF RIGHT VENTRICLE (KG. METER/MIN.)		ART. O_2 SAT. (PER CENT)		ART. pCO_2 (MM. Hg)		TIDAL AIR (ML.)		VITAL CAPACITY (ML.)		M.B.C. (L./MIN.)	
B	A	B	A	B	A	B	A	B	A	B	A	B	A
283	160	0.544	0.370	98.1	—	34	36	—	—	—	—	—	—
588	326	0.123	0.112	99–	—	—	—	—	—	—	—	—	—
130	112	0.537	0.310	90.9	95.5	40	40	700	1,150	4,100	4,100	90	94
92	67	1.107	0.483	92.6	94.9	37	36	1,100	1,650	3,750	3,800	92	98
344	120	1.267	1.246	93.5	95.6	44	43	700	700	2,000	2,100	44	50
108	76	0.602	0.427	95.6	96.2	45	43	750	750	3,050	3,000	48	61
193	104	0.306	0.220	98.2	92.4	40	39	500	550	2,550	2,700	26	26
281	127	1.060	1.060	97.7	97.7	38	38	1,000	1,250	3,000	2,950	69	80
100	129	1.881	2.060	94–	91.4	40	39	1,200	1,300	4,000	4,000	—	—
124	80	1.505	0.869	94.2	94.2	40	38	1,100	1,100	2,550	2,650	40	38
751	218	1.705	0.557	92.7	90.2	28	27	950	700	3,350	2,850	60	68
—	—	—	—	95.6	95.6	26	26	2,000	1,800	3,950	3,750	56	56
105	95	2.193	1.235	82.5	82.5	25	25	800	900	3,350	3,650	86	100
—	—	1.485	1.359	89.3	89.3	42	30	1,100	1,000	2,800	3,000	38	38
316	324	1.682	1.311	91–	91–	33	32	550	550	1,400	1,600	44	44
—	—	2.285	1.797	91.3	—	39	—	850	850	1,400	1,600	16	18
189	150	0.388	0.392	93.6	97.9	—	—	—	—	—	—	—	—
179	128	0.694	0.335	90.8	90.8	40	40	550	1,000	2,500	2,600	32	40
67	40	1.113	1.196	89–	85.4	43	42	850	900	2,600	3,000	42	43
100	105	0.643	0.530	95.6	95.7	43	36	750	750	2,450	2,700	12	30
1428	—	3.284	2.721	42–	43.5	54	48	500	550	1,300	1,300	26	29
$\bar{x}$ = 232.4		$\bar{x}$ = 1.22		$\bar{x}$ = 89.93		$\bar{x}$ = 38.5		$\bar{x}$ = 886		$\bar{x}$ = 2,783		$\bar{x}$ = 48.3	
$\bar{y}$ = 138.9		$\bar{y}$ = 0.93		$\bar{y}$ = 89.99		$\bar{y}$ = 36.6		$\bar{y}$ = 969		$\bar{y}$ = 2,853		$\bar{y}$ = 53.7	
$\bar{z}$ = 93.5		$\bar{z}$ = 0.29		$\bar{z}$ = −0.06		$\bar{z}$ = 1.9		$\bar{z}$ = −83		$\bar{z}$ = −70		$\bar{z}$ = −5.4	
t = 2.765		t = 3.745		t = 0.093		t = 2.433		t = 1.644		t = 1.455		t = 3.810	
0.02>P>0.01^{x}		0.01>P>0.001^{xx}		P>0.90		0.05>P>0.02^{x}		0.20>P>0.10		0.20>P>0.10		0.01>P>0.00	

M.B.C. = Maximum breathing capacity.

In our patients the pulmonary artery pressure fell in spite of a slight increase in blood flow, so that the fall in pulmonary artery pressure apparently cannot be explained by this mechanism.

2. *Changes in Blood Flow Through Collateral Channels Between the Bronchial and Pulmonary Circulations.*—The enlarged bronchopulmonary venous anastomoses, demonstrated by Ferguson and co-workers[20] in patients with mitral stenosis, will, by reversal of flow, be able to deviate blood from the overloaded pulmonary veins to the bronchial veins and to the right atrium. Dulfano and associates[1] feel that this mechanism might explain some of the pressure fall in the pulmonary artery following TED.

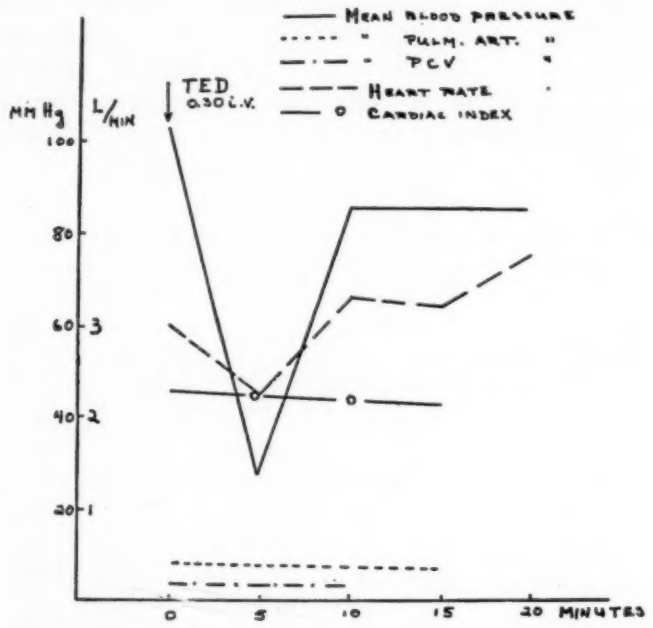

Fig. 1.—Brachial, pulmonary artery, and pulmonary capillary venous pressure, heart rate, and cardiac output in Patient No. 17, E. P.

It is difficult to see how such a shunt mechanism could explain the pressure fall in our patients, since the fall was equally pronounced in patients with lung diseases, where the collateral circulation is probably from bronchial to pulmonary arteries.[21,22]

3. *Changes in Heart Rate.*—Changes in heart rate may, by shortening of the diastolic filling time, give changes in pulmonary blood pressure. This was demonstrated by Aitchison, Cranston and Priest[23] studying the effect of hydralazine in patients with mitral stenosis. The moderating effect which increase in heart rate has on the pressure fall in the pulmonary artery was observed after phentolamine by Storstein, Elgvin, Helle and Sebelien.[24]

In our patients the heart rate increased, and therefore cannot have attributed to the pressure fall in the pulmonary artery. However, as mentioned, the increase in heart rate may have modified to some extent the pressure fall in the pulmonary artery.

4. *Bronchomotor Tone.*—Rodbard[10] has expressed the view that bronchomotor tone, effecting changes in bronchial diameter and ventilation, will influence the pulmonary circulation. He postulates that with bronchial constriction there will be an increased alveolar pressure with consequent narrowing of the pulmonary capillary bed, which will induce a pressure rise in the pulmonary artery. Conversely, bronchial dilatation will open the capillary bed by reducing the intra-alveolar pressure. So far there are only animal experiments to support this view.

The increase in maximal breathing capacity suggests that TED induces a bronchial dilatation, which may have reflected a decrease in bronchomotor tone. This decrease in bronchomotor tone may have induced the pressure fall in the pulmonary artery and the decrease in pulmonary arteriolar resistance, by the

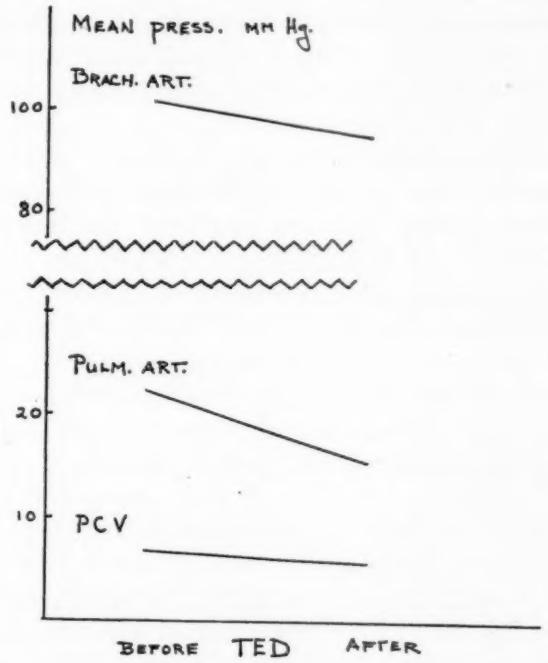

Fig. 2.—Changes in brachial artery, pulmonary artery and pulmonary capillary venous pressure following 0.30 Gm. TED intravenously.

mechanism mentioned. We have calculated, therefore, the correlation coefficients between changes in maximal breathing capacity and changes in pulmonary artery pressure and in pulmonary arteriolar resistance. In neither instance was there any significant correlation, the correlation coefficients being, respectively, 0.11 and −0.29. Although admittedly more factors than bronchoconstriction enter into the maximal breathing capacity, and although the reproducibility of the method is not very good, this study does not lend support to Rodbard's view.

5. *Changes in Pulmonary Arteriolar Tone.*—A direct dilating effect on the pulmonary blood vessels cannot be established unless it is known that the agent has no effect on blood flow, heart rate, bronchial tone, and systemic blood pressure (Daly[25]). There is now considerable evidence of a constricting effect of

anoxia on pulmonary blood vessels[26] and of a dilating effect of oxygen.[27] The pressure rise in the pulmonary artery during anoxia is to some extent independent of changes in blood flow. There is also strong evidence that acetylcholine has a dilating effect on the pulmonary arterioles in some patients with mitral stenosis,[28] in anoxemia,[29] and in primary pulmonary hypertension.[30] Epinephrine, on the other hand, does not produce a consistent increase in pulmonary arteriolar resistance, but a concomitant increase in pulmonary artery pressure and blood flow.[31] Norepinephrine is similar.[32] The increase in pulmonary artery pressure produced by the latter is interpreted as being due to an increase in pulmonary venous pressure.

The pressure fall in the pulmonary artery is far more pronounced than that in the pulmonary capillary (Fig. 2). As we have seen there is no evidence to indicate a passively induced pressure fall in the pulmonary artery; hence, we may conclude that this pressure fall is mediated through a fall in pulmonary arteriolar resistance. We assume this to be a humoral action, in the same way as are the other actions of TED.[16]

Although the response of the pulmonary circulation to TED injection in the patients reported here is in accord with the findings of Dulfano and co-workers[1] in patients with mitral stenosis, it is not in accord with the findings of Werkø and Lagerløf[4] in patients with hypertensive cardiovascular disease. The latter investigators observed a pronounced increase in cardiac output, but no consistent fall in pulmonary arteriolar resistance. The different behavior in patients with mitral stenosis and patients with hypertension has been noted previously by Howarth, McMichael and Sharpey-Schafer.[6] The cause of the difference is not known, but we know that various etiologic types of heart disease show different reactions to other cardiovascular drugs, such as digitalis.

Both Starr and co-workers[7] and Fowell and associates[2] observed an increase in left ventricular work in their patients with heart failure following TED. Werkø and Lagerløf found no change in work per beat of the left ventricle, but as the heart rate increased, the work calculated per minute must have increased. Thus it might be argued that TED could be of doubtful value in arteriosclerotic heart disease, inasmuch as its coronary vasodilating action might be counteracted by increased work of the heart, induced by the increase in cardiac output. Dulfano and co-workers found, as we did, a decrease in the work of the right ventricle. We have not calculated the work of the left ventricle in our material, but, as there was no significant change in cardiac output and the blood pressure in the systemic circulation fell, there certainly also was a fall in the work of the left ventricle, although to a lesser extent than in that of the right ventricle. We may conclude that in our patients with various heart and lung diseases, TED did not add any extra load to the work of the heart; on the contrary, it lessened the burden on the heart muscle.

SUMMARY

1. In a group of patients with various heart and lung diseases, exclusive of hypertensive heart disease, a study of the ventilatory and circulatory effect of theophylline ethylenediamine has been carried out.

2. TED gave a distinct increase in maximal breathing capacity, indicating a bronchodilating effect. This improved ventilation lowered the arterial pCO_2, while the arterial O_2 saturation was unchanged.

3. TED increased the heart rate and decreased the blood pressure, both in the systemic and in the pulmonary circulations (more pronounced in the latter). The cardiac output and the pulmonary capillary venous pressure was unchanged, and there was a pronounced fall both in peripheral arterial and in pulmonary arteriolar resistance.

4. It is concluded that this pressure fall was mediated through a direct dilating effect of TED on the arterioles, both of the pulmonary and systemic circulations.

5. The work of the right ventricle showed a fall. This indicated that TED in this group of patients lessened the burden of the load placed on the right ventricle by pulmonary hypertension.

6. Compared to earlier investigations there seems to be a different reaction to TED in this group of patients and in patients with hypertensive cardiovascular disease. In the latter group the most pronounced effect was the increase in the cardiac output, while the vasodilating action on the pulmonary circulation was insignificant.

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The Hemodynamic Results of Open Heart Surgery: Preliminary Report

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After considerable experience (110 cases), and a low mortality rate with open heart surgery, using a pump oxygenator, it is our opinion that the blind techniques for the surgical correction of congenital heart disease are now archaic. It is the purpose of this paper to show the consistent dramatic improvements in hemodynamics after corrective open heart surgery which were not obtained, as a rule, in the blind techniques.

The following data have been obtained from catheterizations carried out preoperatively and from 6 to 12 months postoperatively in order to assess the results of corrective open cardiac surgery. All survival cases are scheduled for postoperative cardiac catheterization studies, sometime after the lapse of 6 months or more. The results discussed are the preliminary studies of a series of cases taken from our first group of patients submitted to open heart surgery.

INTERATRIAL SEPTAL DEFECT

Table I summarizes the results in 10 cases of interatrial septal defect operated upon by the open heart method.

As can be seen, the oxygen saturation of the arterial blood rose in all but one case. In all cases there was complete closure of the defect, as adjudged from oxygen content samples from at least 3 auricular positions when compared with the samples from the superior and inferior venae cavae. In those patients who had developed minor to moderate hypertension of their lesser circulation, these pressures had returned to normal levels by the end of 6 months to 1 year.

Our surgical mortality statistics in a series of 16 cases was 6.2 per cent. Certainly no one will deny that seeing the defect makes complete surgical correction probable, much more so than blindly feeling and haphazardly sewing the defect closed.

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TABLE I. HEMODYNAMIC RESULTS OF OPEN HEART SURGERY IN INTERATRIAL SEPTAL DEFECTS

CASE	AGE		BLOOD OXYGEN CONTENTS (VOLS. %)					ARTERIAL SATURATION (%)	SHUNT FLOW (%)	PRESSURES (MM. Hg)			
			SVC AND IVC / 2	RA	RV	PA	FA			RA	RV	PA	FA
J. H.	12	Preop.	8.7*	11.4	12.4	12.6	12.2	89.0	+70	9/6	40/0	40/18	109/61
		Postop.	11.6	12.2	11.1	—	15.0	94.0	—	6/4	30/—2	—	110/70
M. K.	42	Preop.	11.3	14.1	14.0	—	15.2	91.0	69.3	13/9	55/10	—	150/90
		Postop.	11.2	11.7	11.6	11.6	16.0	95.0	—	5/1	23/0	23/12	130/70
C. D.	6	Preop.	8.7	12.6	12.5	13.5	14.5	96.0	82.8	6/1	40/0	19/7	120/68
		Postop.	9.7	11.3	—	10.7	—	—	0	6/2	20/—1	17/5	—
R. M.	13	Preop.	13.2	15.3	15.4	15.3	16.4	97.0	64.5	6/3	25/0	17/7	115/70
		Postop.	13.2*	12.2	12.6	12.3	17.2	99.0	—	5/2	18/0	18/7	110/65
E. F.	42	Preop.	10.0	13.1	13.2	13.1	14.3	94.0	72.1	15/3	37/7	40/10	145/75
		Postop.	9.6	9.8	9.7	9.8	13.7	94.0	—	4/1	18/0	18/8	115/65
G. B.	8	Preop.	13.5*	16.3	16.8	17.5	17.5	93.0	+70	11/3	35/2	27/12	120/60
		Postop.	12.7	13.1	12.1	—	15.5	97.0	—	5/3	18/1	—	105/65
R. T.	12	Preop.	11.5	13.4	13.6	13.6	14.6	95.0	67.8	19/9	35/6	23/8	120/56
		Postop.	12.7	12.8	13.6	13.4	15.7	96.0	—	11/—1	28/1	28/10	100/55
L. L.	8	Preop.	9.5	14.1	14.4	14.2	15.2	99.0	82.5	7/2	24/5	17/14	110/75
		Postop.	9.4*	9.5	8.4	—	—	—	—	4/2	28/2	—	—
M. K.	12	Preop.	14.0	16.7	15.7	16.0	17.9	99.0	51.3	9/3	42/5	20/12	—
		Postop.	10.2	10.5	10.3	10.2	15.0	85.0	—	3/1	22/0	13/5	115/60
G. J.	12	Preop.	12.0	15.7	15.5	—	16.2	99.0	83.4	9/6	40/3	—	115/75
		Postop.	11.7*	13.9	13.8	13.7	17.3	100	—	9/4	18/0	17/9	100/60

*Superior vena cava only.

PULMONIC STENOSIS

Table II summarizes the hemodynamic data in 3 cases of pulmonic stenosis operated upon by the open heart method.

TABLE II. HEMODYNAMIC RESULTS OF OPEN HEART SURGERY IN PULMONIC STENOSIS

Cases Age (yr.)	T. P. 7		J. G. 2		N. S. 8	
Pressures (mm. Hg)	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
RA	12/7	7/1	10/5	9/3	8/3	10/3
RV	180/20	30/−2	96/4	27/0	90/5	32/1
PA	18/13	19/5	18/10	19/7	16/10	30/11
FA	112/56	92/50 (cuff)	92/60	—	131/81	105/70
Arterial saturation (%)	94.0	—	92.3	—	96.0	96.6

As can be seen, all cases had an elevated right ventricular pressure, which at restudy following the surgery had returned to a normal level. There was a very small residual gradient across the valve (10 mm. Hg) in 2 of the cases.

Here again the value of the open heart technique appears to be far superior, with a mortality of 0 per cent in 12 cases.

INTERVENTRICULAR SEPTAL DEFECT

Table III summarizes the results in 7 cases of interventricular septal defect. In 3 cases the defect was not completely closed, because of technical difficulties encountered in the development of the techniques for closure, i.e., sutures pulling out before the use of Ivalon patches, and Ivalon patches being too porous. In one case, although oxygen studies showed the defect closed, there was no change in lesser circulation pressures, due to what we feel were irreversible changes in the pulmonary vasculature, changes which we have discussed adequately elsewhere.[1,2]

In the 3 cases which were adequately and technically closed, an analysis of the hemodynamic data by oxygen sampling showed the defect closed and a return of pulmonary arterial pressures and right ventricular pressures to normal levels.

The problems in interventricular septal defect are more complex, and it is gratifying to see reversal of the elevated pressures to a normal level in the 3 patients so far studied. In a series of 29 cases, our over-all mortality has been 27.6 per cent. In fairness, it must be pointed out that many of these cases were in far advanced states of their disease.

CONCLUSIONS

From an analysis of the foregoing data it would appear that open cardiac surgery by means of a pump oxygenator in interatrial septal defects, pulmonic

TABLE III. HEMODYNAMIC RESULTS OF OPEN HEART SURGERY IN INTERVENTRICULAR SEPTAL DEFECTS

CASE	AGE		BLOOD OXYGEN CONTENTS (VOLS. %)					ARTERIAL SATURATION (%)	SHUNT FLOW (%)	PRESSURES (MM. Hg)			
			SVC AND IVC / 2	RA	RV	PA	FA			RA	RV	PA	FA
P. S.	9	Preop.	10.7	11.2	14.4	13.8	14.6	93.4	78.4	14/11	68/2	68/24	128/64
		Postop.	12.8	13.4	13.2	13.5	16.6	97.3	—	7/1	57/0	46/12	106/55
J. L.	7	Preop.	5.9	5.6	7.8	—	8.8	86.3	67.8	12/8	80/4	—	108/78‡
		Postop.	6.9*	7.5	8.7	8.7	10.4	86.5	52.6	4/1	25/0	23/10	—
R. P.	4	Preop.	6.9	6.8	8.6	8.8	9.7	92.4	69	6/1	54/—4	56/20	86/44
		Postop.	6.5	7.7	11.3	11.2	—	—	—	12/6	44/0	40/12	—
J. M	28	Preop.	13.2	14.5	15.9	16.3	18.1	93.9	60	8/3	70/3	72/35	108/62
		Postop.	13.6*	14.6	17.8	17.8	19.4	93.6	70.4	7/5	63/1	62/36	115/65
B. M.	4	Preop.	8.3	8.3	12.0	11.1	12.3	94.0	70	10/7	80/8	80/26	108/68
		Postop.	8.2*	10.1	10.5	10.2	12.8	90.2	—	10/8	74/10	75/40	100/60
P. R.	2½	Preop.	8.4†	8.0	10.2	9.3	10.8	91.5	48.1	8/5	80/12	88/48	—
		Postop.	8.7*	10.2	9.6	9.5	13.0	95.9	—	3/1	17/0	15/5	85/55
J. R.	8	Preop.	10.1	10.3	12.2	11.9	13.9	93.4	48.8	9/4	38/6	27/12	88/64
		Postop.	12.4*	12.3	11.7	11.5	15.5	89.0	—	5/1	20/0	19/10	110/65

*Superior vena cava only.
†Inferior vena cava only.
‡Aorta.

stenosis, and interventricular septal defects can, in the majority of cases, return the altered hemodynamics to a completely normal profile, and as such, in all probability, insure to the patients a prolonged longevity as far as their congenital heart disease is concerned. The over-all mortality is low and is certainly acceptable by present standards.

Helen Klienhenz, R.N., and Marjorie McIntyre, R.N. aided in this study.

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Primary Hypertension and Hypertensive Disease in Early Childhood

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INTRODUCTION

It has been suggested that "essential hypertension" and hypertensive disease of adults may, in certain cases at least, begin during childhood. Instances of hypertension in children, however, have been described as "rare"[1,2] and pediatricians, therefore, frequently fail to measure the blood pressure.

In areas where determination of the blood pressure is included as a routine part of a child's physical examination, the consulting internist may find a surprising number of hypertensive children among his referral cases. Within the past 5 years, 11 hypertensive subjects under 10 years of age have been referred to the Hypertension Service for evaluation. Four of these cases, after completion of laboratory studies, failed to show evidence of an underlying organic cause for their blood pressure elevation. The following report emphasizes the clinical aspects of primary hypertension in these children, and the need for blood pressure determination as an important part of a child's physical examination.

CASE REPORTS

CASE 1.—P. R.* This child was found to have an apical systolic murmur at the age of 3 months. There had been no history of cyanosis, dyspnea, edema or other abnormality. He had gained weight satisfactorily and his appetite was excellent.

At the age of 5 months he was admitted to the hospital for further evaluation. The history was not remarkable save for hypertensive disease in the maternal grandparents.

Physical Examination.—The data showed: pulse, 120; respirations, 25; blood pressure (in mm. Hg), 120/80 in the right arm, 130/90 in the left arm, 150/120 in the left leg, and 140/120 in the right leg. The weight was 6,560 grams. The measurements were: head, 42 cm.; chest, 42 cm.; stem, 44 cm.; total length, 65 cm. The patient was well developed, well nourished, somewhat irritable, appearing neither acutely nor chronically ill and in no distress. The remaining positive findings were restricted to enlargement of the heart, the border of dullness being 6 cm. from the mid-sternal line in the sixth intercostal space.

Laboratory Data.—The urine was entirely normal. Blood data included: hemoglobin 14 Gm.; red blood cells 4,600,000; platelets adequate; white blood cells 10,500 with normal differential; blood urea nitrogen 16 mg. per cent; blood sugar normal; cholesterol 145 mg. per cent.

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*The blood pressure in Patient P. R. was measured with the "infant size" (1.0 inch) sphygmomanometer cuff. The "child's cuff" (3.0 inches) was used for measurement in the other patients.

The usual flora was found in the nose and throat. The spinal fluid was normal. Fluoroscopy revealed symmetrical cardiac enlargement. I.V.P. was unsatisfactory. Cystogram was normal. Retrograde pyelograms were normal bilaterally. A chest x-ray showed scoliosis at T_9 and T_{10}, and questionable enlargement of the cardiac silhouette. The skull was normal. An ECG was within normal limits.

Course in the Hospital.—The patient had an asymptomatic and afebrile course, with hypertension persistent at or considerably above the levels found initially. Otherwise the evaluation was considered entirely normal, and numerous consultants agreed that there was no evidence of primary disease responsible for the hypertension. He was discharged on the eleventh hospital day.

Follow-Up.—The blood pressure continued at ranges described for 1½ years, then subsequently was found at normal levels of 70-85/40-55 mm. Hg.

CASE 2.—E. L., a 5½-year-old white boy with Recklinghausen's disease of 4 years' duration, was found to have a blood pressure which ranged from 195 to 145 mm. Hg systolic and 120 to 130 mm. Hg diastolic. The history was not revealing except that the mother also had mild neurofibromatosis. The family history was negative for hypertensive disease.

Physical Examination.—The blood pressure (in mm. Hg) was 190/120 in the right arm, 185/195 in the left arm, and 200/140 in the right leg. Peripheral pulses were all somewhat forceful. Examination of the heart revealed the point of maximal impulse at the nipple line. Three heart sounds were audible; the first and second heart sounds were sharp, and the third, just preceding the first sound, was followed by a short presystolic murmur. A Grade 2 systolic murmur was present over the pericardium. Examination of the eye ground revealed normal fundi. Except for the facial neurofibroma, the remainder of the physical examination was within normal limits for a 5-year-old boy.

Laboratory Data.—Examination showed a urine concentration of 1.025. Protein and sugar were negative. Blood data included hemoglobin 10.5 Gm.; red blood cells 4,700,000; white blood cells 10,600 with 42 per cent lymphocytes, 2 per cent monocytes, 8 per cent eosinophils, and 48 per cent mature polys. The Mazzini test was negative. Blood urea nitrogen, 12 mg. per cent; sugar, 79 mg. per cent; chloride, 97; protein, 7.5; calcium, 10.1; phosphorus, 3.9; potassium, 4.8. The prothrombin time was 34 seconds (control 40 seconds). Phenolsulfonphthalein showed 55 per cent excretion after 15 minutes; 72.5 per cent excretion after 2 hours. I.V.P. was normal. A chest x-ray was negative. The ECG was within normal limits, showing slight left ventricular predominance. Provocative tests to rule out the possibility of pheochromocytoma (histamine and benzodioxane) were all negative.

The patient has had 8 subsequent readmissions over a period of 6 years; each time he readily tolerated the surgical operations (removal of a part of the neurofibroma). The hypertension has persisted at the same general range without symptoms or evidence of progression.

CASE 3.—G. H.* Seven months before his first admission to the hospital, this 6-year-old white boy had an acute episode of vomiting, lasting 24 hours, and unassociated with other symptoms. Subsequently, he was well until 6 months later, at which time his mother noticed that his urine was suddenly red in color. A urine specimen was analyzed by his physician and found to contain many "red cells." This episode of "bloody urine" lasted 36 hours and returned 1 week later for 24 hours. There were no symptoms at this time and no abnormal findings on physical examination, although the blood pressure was not determined.

Three weeks before admission a second 24-hour episode of vomiting occurred; it was associated with headache and acute abdominal pain. He was hospitalized for 3 days, received intravenous fluids, and recovered rapidly. After this, he tired easily, and the mother noticed that his heart "pounded" visibly in his chest. His appetite remained good, and he lost no weight. Three weeks after the second episode of vomiting, the blood pressure, measured for the first time, was found to be 250/170 mm. Hg, and admission to the hospital was advised. There had been no frequency of urination, except immediately preceding the first episode of hematuria, no dysuria, known fever, history of recurrent upper respiratory infections, or sore throat.

*The authors are grateful to Dr. Henry P. Goldberg for referring Patient G. H. to us, and allowing us to include him in this report.

Past History.—The boy was a spontaneous full-term delivery. At birth he weighed 5 pounds and 4 ounces, and the fingers on the left hand were noted to be completely webbed, excluding the thumb. His subsequent development was that of a normal boy up until the onset of the present illness.

Family History.—The mother developed hypertension and albuminuria during the last month of pregnancy but had normal delivery with no further complication. The family history was otherwise unremarkable.

Physical Examination.—Data on the day of admission showed: temperature, 38.4°C.; pulse, 128; respirations, 20; blood pressure (in mm. Hg), 250/170 in the right arm and 260/200 in the right leg. The patient was a slim but well-nourished lad, not appearing ill. The pupils were described as "asymmetrical," and fundal arterioles were tortuous and narrowed, with numerous "nicking" of venules; there was neither papilledema nor hemorrhages. The heart showed regular sinus rhythm; the point of maximal impulse was felt in the fifth intercostal space, 6 cm. to the left of the mid-sternal line, with a very forceful impulse. The second aortic sound was loud and snapping, and a high-pitched, short systolic murmur was heard at the base. The lungs were clear to percussion and auscultation, and the pulse was pounding in all extremities. There were no masses, tumor, or evidence of fluid in the abdomen. The initial impression on admission was that of a possible kidney tumor of unknown type, with hypertension and hematuria, or acute glomerular nephritis.

Laboratory Data.—The ECG showed A-V nodal rhythm, P-R interval of 0.09 sec., and QRS-T of 0.06 sec. On the chest x-ray, "minimal cardiac enlargement," primarily left ventricular in type, was demonstrated. Urine examination showed: specific gravity 1.020; acid reaction; 3+ protein; no sugar; no clumped white cells; rare red cells; rare white cells; rare hyaline casts. The Mazzini test was negative. Blood data included: hemoglobin 12.0 Gm.; red blood cells 5.6; platelets, adequate; white blood cells 10.2, with 24 lymphs, 2 secs., 70 mature polys, and 3 bands. Sedimentation rate: 7.3 (albumin 5.9), globulin 1.4; blood cholesterol 302 mg. per cent. Catheterized urine from the right ureter showed: at 2 minutes 126 mg. per cent of urea nitrogen per 100 c.c. of urine, at 30 minutes 68 mg. per cent of urea nitrogen per 100 c.c. of urine. Catheterized urine from the left ureter showed: at 2 minutes 87 mg. per cent of urea nitrogen per 100 c.c. of urine, at 30 minutes 68 mg. per cent of urea nitrogen per 100 c.c. of urine. Urine from the left ureter contained a gross amount of red blood cells and 1-2 white blood cells; that from the right ureter contained an occasional red blood cell and 1-2 white blood cells. Cultures of urine from both ureters were negative. There were occasional fine granular casts present bilaterally. Phenolsulfonphthalein appeared in the urine from each ureter within 2 minutes after injection; at 30 minutes, the right kidney eliminated 18 per cent, and the left kidney, 23 per cent. Several intravenous pyelograms showed prompt function without anatomic defects. A right retrograde pyelogram was unremarkable; a left retrograde pyelogram showed no evidence of filling defect, but the calyceal system was smaller than that on the right. Pharmacologic tests for a pheochromocytoma (benzodioxane) were negative. An x-ray of the skull was normal.

It was the general opinion of the urological consultants that the left kidney was abnormal. For this reason it was removed, with exploration revealing a normal adrenal gland. The histologic examination indicated only calcification of a considerable number of renal tubules in the periglomerular regions and in the papillae. The postoperative course was not remarkable, and the patient was discharged with persistent hypertension of severe degree after 1 month of hospitalization. For the next 7 months he was followed in the clinic, with the blood pressure ranging from 170 to 230 mm. Hg systolic and 110 to 150 mm. Hg diastolic. Over the last 2 months he displayed 3 episodes of left facial weakness, with inability to speak and severe generalized headache. Physical examination showed a persistent right facial weakness, with a blood pressure of 205/140 mm. Hg in the right arm, seated, and 204/130 mm. Hg in the left arm. Increased narrowing and tortuosity of fundal vessels was noted to be bilateral but was more severe in the left fundus.

Second Admission.—Readmission, 7 months after discharge, was advised for evaluation of sudden and persistent vomiting of 6 hours' duration. The blood pressure was 300/200 mm. Hg in the right arm; pulse, 160; respirations, 28. The right palpebral fissure was wider than the left but the pupils were normal. Since the clinical picture was that of an acute hypertensive crisis, the patient was treated with intravenous and intramuscular magnesium sulfate (4 c.c. of 50 per

cent solution). On the following day the blood pressure was 220/90 mm. Hg and the patient was resting comfortably without nausea.

Laboratory Data.—The urine showed 2+ protein and occasional red blood cells in the sediment. The blood urea nitrogen was 30 mg. per cent, falling in 7 days to 20 mg. per cent on bed rest. Other laboratory findings, repeating those studies of the first admission, were within normal limits.

Course in the Hospital.—Within 3 days after admission the symptoms had completely subsided; the patient was discharged on the eleventh day with the blood pressure still greatly elevated.

Follow-Up.—Over the following 6-month period, the behavior of the boy became unusual. He "argued" viciously (in the mother's words) with his parents and sister, and behaved in a hyperirritable and hyperkinetic manner most of the time. On one occasion he became extremely excited and complained of a severe headache, "screaming" violently. Within 2 to 3 hours he felt nauseated and remained in this acutely disturbed state for the next several days.

Third Admission.—Because of the above-mentioned episode, he was readmitted to the hospital. Upon examination both pupils appeared dilated widely but reacted to light and accommodation. The blood pressure was 290/210 mm. Hg in the right arm, and the remainder of the physical findings were not dissimilar from those noted beforehand.

Laboratory Data.—The urine had 2+ protein and occasional red blood cells in the sediment. Other laboratory findings were within normal limits. In spite of repeated negative tests for pheochromocytoma (benzodioxane, Priscoline, and plasma bio-assay) on all admissions, the clinical history seemed sufficient to warrant abdominal and thoracic exploration; this was carried out without evidence of any such tumor being found. A thoracolumbar sympathectomy from T_9 to L_3 was carried out on the right side. Pathologic studies on the arterioles in ganglionic tissue obtained at the operation showed thickened walls and narrowed lumina, with the comment that "the arteriolar lesion in this biopsy is ill defined."

Postoperative Course.—The patient developed a postoperative anemia requiring three transfusions of 250 c.c. each. In addition, a right hemiparesis developed, with definite facial weakness on the left side. The blood pressure postoperatively fell to a level of 150/90 mm. Hg, although within 24 hours it rose steadily to 200/150 mm. Hg. The general hemiparesis gradually improved in the 10-day postoperative period, but facial weakness showed little if any change. He was discharged 14 days after admission, with plans to readmit him for the second stage of the sympathectomy.

The patient's condition did not improve sufficiently to warrant the operative procedure. His nutrition and appetite were unimpaired, but repeated violent headaches associated with nausea and vomiting occurred about 10 to 14 days following discharge. Approximately 5 months later the patient complained of an unusually severe bilateral generalized steady headache with prominent dysphagia. Coma developed, and the mother noted that right hemiparesis, which had been absent since his discharge from the hospital, had suddenly returned. The patient was admitted to a nearby hospital, but he expired shortly without recovering consciousness. Permission for a post-mortem examination was not obtained.

Case 4.—J. J., a 9-year-old white boy, was admitted for evaluation of hypertension of 4 months' duration which was discovered at a routine pre-camp physical examination. His blood pressure had never been taken previously. The child, entirely asymptomatic at the time of admission, was well developed, well nourished, alert, and cooperative. The entire physical examination was negative, except for the blood pressure which was 164/128 mm. Hg in the right arm and 200/150 mm. Hg in the left leg.

Laboratory Data.—A large number of laboratory studies, including several x-rays of the chest and renal system, ECG, urine examination, and urine assay for epinephrine substances, were negative. As in Case 3 pharmacologic tests for pheochromocytoma (benzodioxane) were negative. It is of interest to compare these two cases as far as the symptomatology and the laboratory findings are concerned.

Course in the Hospital.—The patient had an asymptomatic, afebrile hospital course. The blood pressure was persistently high and ranged between 160 and 140 mm. Hg systolic, and 118 and 110 mm. Hg diastolic. A diagnosis of essential hypertension was made and the patient was subsequently discharged.

Second Admission.—He was readmitted 2 years later for repair of a right inguinal hernia, at which time the blood pressure was again between 160 and 140 mm. Hg systolic and 128 and 110 mm. Hg diastolic in the arms, and was 200/150 mm. Hg in the legs. The entire physical examination at the time of his second admission was negative.

Laboratory Data.—The urine showed 1+ protein (on Addis count there was 0.04 Gm. of protein in the urine of a 12-hour specimen of 370 c.c.). The ECG showed a pattern compatible with left ventricular hypertrophy. A chest x-ray was within normal limits.

Postoperative Course.—The patient tolerated the surgical procedure for the repair of the hernia very well, and it was of interest that under general anesthesia, his blood pressure ranged between 130 and 140/100. The postoperative course was uneventful and the patient was discharged on his second postoperative day.

DISCUSSION

Hypertension in children, in the great majority of instances, is found with renal disease.[1] Although in acute glomerulonephritis the incidence of hypertension is high (60 to 70 per cent), its causes are not known and, hence, many theories have been presented as to its mechanism.[3] It has been suggested that in children, chronic pyelonephritis is more frequently a cause of hypertension than is chronic glomerulonephritis, and that in some cases the elevation of the blood pressure will respond to urologic management if the hypertension is detected in its early stage before the onset of irreversible renal damage.[4,5] In most instances in which a child is investigated for persistent hypertension, the ultimate cause is therefore thought to be of renal origin. Unilateral renal disease (especially pyelonephritis) deserves special attention as a possible cause of persistent hypertension, although it is worth emphasizing that a large number of patients with unilateral renal disease remain normotensive. Hypertension is not uncommon in cases of Wilm's tumor,[6-8] and one patient with this disorder was excluded from our study.

Aside from the patients whose blood pressure may rise when they are emotionally disturbed (physical examination in children, mental or physical distress, etc.), hypertension may be associated with certain neurological disorders.[9,11,12] Increased intracranial pressure from a variety of causes may produce hypertension, although with this condition resulting from a brain tumor (or subdural hematoma) the blood pressure elevation may not be fixed.[10]

In cases of hypertension in children and young adults, one should always think of the possibility of coarctation of the aorta. This clinical entity is well recognized and the diagnosis is, in most instances, not complicated. Mechanisms of the hypertension may not be solely anatomic, for renal, humoral, and neurogenic factors have been implicated.[13] Other disorders of the heart and the great vessels in children may be accompanied by hypertension. Heart failure, arteriovenous fistula, particularly patent ductus, polycythemia, etc., should always be considered.

Certain endocrine disorders may be associated with an elevated blood pressure; hyperthyroidism, disturbances of adrenal cortical function, pheochromocytoma, ovarian agenesis, etc., are fairly well known as a cause of hypertension.[16,17] There is some relationship between certain forms of hypertension and the adrenal cortex. Desoxycorticosterone acetate in animals, normal patients, or patients with Addison's disease may produce blood pressure elevation.[18-21]

Adrenalectomy, on the other hand, reverses the hypertension following a partial renal artery ligation, and adrenalectomized dogs are insensitive to renin.[22] In attempts to explain the mode of action of thiocyanate, Healy[24] has demonstrated high concentration of this drug in the adrenal cortex of rabbits, in line with this possible relationship. Cushing's syndrome may be encountered with hypertension in children. At least 26 cases, all due to adrenal tumor, have been reported in children under 10 years of age.

A tumor of chromaffin tissue of the adrenal medulla (pheochromocytoma) which liberates excessive amounts of epinephrine and/or norepinephrine[27-32] may also result in hypertension. Pheochromocytoma is uncommon, and, if present, may be associated with either persistent or paroxysmal hypertension.[33] Benzodioxane and Regitine tests are of value as diagnostic aids,[34,35] and further studies on catechol excretion should be made to aid in establishing the diagnosis.[36,37]

Essential hypertension in childhood is relatively uncommon. By definition, it is an elevation of blood pressure for which no definite underlying organic cause can be demonstrated; therefore, the diagnosis should be made by a process of careful exclusion. The cases reported in this article were considered to have essential hypertension because such primary causes could not be found. Repeatedly negative Regitine and benzodioxane tests, except for Patient P. R., and the subsequent course of events in follow-up on each patient substantiate the probable "essential" nature of their hypertension. It is of interest in view of the familial tendency in hypertension,[38-40] that of the 4 cases cited, only 1 parent (Case 3) displayed hypertension.

A malignant phase of hypertension, accompanied by arteriolar sclerosis, has been observed in children. Dawson and Nabarro[41] have reported a male infant with intimal hyperplasia of the arteries and arterioles associated with severe hypertension. The arterioles also demonstrated a varying amount of reduplication of the internal elastic lamina. According to their report, the infant died of hypertensive heart failure. Certain aspects of our Case 3 compare favorably with the clinical manifestations which they describe. According to Ford,[10] arteriolar sclerosis is more common in children over 6 years of age. He does not indicate either sex predominant and believes that the disease is not familial.

It is important to bear in mind that if renal insufficiency secondary to hypertension develops in such children, pathologic changes similar to those found in adults (arteriolar sclerosis, degeneration and necrosis of vessels and tissues supplied, and progressively rapid impairment of renal function) may be observed.

SUMMARY AND CONCLUSIONS

1. The clinical features are reported in 4 children with apparently primary hypertensive disease.

2. Possible etiological factors concerning hypertension in early childhood are discussed.

3. Essential hypertension in children is not common, but it is emphasized that physicians should be aware of it and check the blood pressure routinely in all subjects, regardless of age.

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Book Reviews

RHYTHMUSSTÖRUNGEN DES HERZENS. By K. Spang, Stuttgart, 1957, Georg Thieme Verlag, 548 pages, 109 illustrations (appendix-111 pages, 228 illustrations).

In his preface the author gives as justification for his book the recent progress in the experimental work and drug therapy of cardiac arrhythmias, after a relative stagnation period following the classic monographs of Lewis (1925) and Wenckebach and Winterberg (1927). Cardiac arrhythmias, of course, are discussed at length in the numerous recent electrocardiographic textbooks, and in monographs presenting new theories, such as Prinzmetal's *Auricular Arrhythmias* or Schaefer's *Das Elektrokardiogramm.*

It is important to know, therefore, in what respect Spang's book differs from the large available literature. First of all, it is not an electrocardiographic textbook limited to arrhythmias, and, secondly, its virtue lies in a critical discussion of the existing hypotheses on the mechanism of arrhythmias rather than in the proposal of new ones. There is, naturally, a considerable degree of overlap with electrocardiographic textbooks, since the documentation is nearly exclusively electrocardiographic. However, the arrhythmias are treated as a clinical problem, including circulatory disturbances, clinical correlations, prognosis and therapy, in addition to discussion of the mechanism. The book is primarily written for the clinician, on the basis of a large and valuable personal experience.

The character of the book may be illustrated by the following examples: (1) The theories of auricular flutter and fibrillation are discussed on 5 pages (pp. 200-205), and (2) the mechanism of ventricular fibrillation on 3 or 4 pages (pp. 221-222). Yet, this condensed discussion gives adequate basic information to follow recent developments. In contrast, 8 pages are allotted for discussion of the Adams-Stokes syndrome which has immediate clinical application.

In the first and largest part of the book (pp. 79-320), the mechanism of the various arrhythmias is discussed, together with circulatory effects and prognosis, and the second part is devoted to clinical correlations (pp. 320-402). In so large a volume, some degree of repetition is unavoidable, but this is kept to a minimum. In the second part, the arrhythmias are discussed from the aspect of their incidence and clinical significance in specific diseases and stress situations. The thirty chapters in this part include the carotid sinus reflex, orthostatic response, exercise, respiration, drug intoxication, cardiac catheterization and surgery, various infections, and systemic and cardiac diseases. The third part of the book (pp. 403-485) is a systematic discussion of the action of various drugs (including cardiodynamic effects) and the clinical applications of these drugs in the treatment of the various types of arrhythmias.

There are two introductory chapters, the first one by W. Doerr, on morphology and pathology of the conduction system, and the second one by W. Trautwein, on the electrophysiologic background, based to a large part on Trautwein's own fundamental work with intracellular electrodes.

This is truly a monumental work with 548 pages of text and literature, 109 illustrations in the text and 228 in an appendix, and over 1,800 references. The quality of the illustrations is excellent, and it is an advantage that the electrocardiograms are recorded with a three-channel machine. Last but not least, the presentation is fluid and easily readable. The book is sufficiently different from other textbooks to recommend it to cardiologists as well as general practitioners.

E. S.

SYSTEMIC ARTERIAL EMBOLISM. By John Martin Askey, M.D., New York, 1957, Grune & Stratton, Inc., 157 pages, 23 figures, and 23 tables.

This monograph is simply a review of the clinical literature dealing with thromboembolic disease of the arteries. There are 281 bibliographic items. At times the text is difficult to follow because of the many numerals, parenthetical expressions, and authors' names. The book is of value as a reference volume.

J. W. E.

Announcements

THE THIRD INTERNATIONAL CONGRESS OF ANGIOLOGY will meet in Venice, Italy, Sept. 25 to 28, 1958. The general theme of the Congress will be the experimental and clinical pathology of the medium and small blood vessels, including arteries, veins, lymphatics, and capillaries.

The Secretary of the Congress is Dr. M. Comel of the Dermatological Clinic, University of Pisa, Pisa, Italy.

The 1958 Meeting of THE AMERICAN GOITER ASSOCIATION will be held in the St. Francis Hotel, San Francisco, June 17, 18, and 19, 1958. Hotel reservations may be secured by writing to the Goiter Housing Bureau, Room 300, 61 Grove Street, San Francisco, Calif. A deposit of $10.00 per room is required.

A RESIDENCY AND RESEARCH FELLOWSHIP IN CARDIOLOGY are being offered at the City of Hope Medical Center in Duarte, California. The Residency will emphasize clinical aspects of diagnosis and treatment of heart disease and cardiac catheterization. The Research Fellowship will provide more detailed training in techniques of physiologic investigation of patients with cardiovascular disorders and also afford an opportunity for the Fellow to devote approximately one half his time to a research project in the animal or clinical laboratories. Candidates must be graduates of approved medical schools and, except in unusual instances, must have completed at least one year of residency training in Internal Medicine for the Residency, and two years for the Fellowship. The Residency is for a period of one year, with salary stipend of $3,600. The Fellowship is for a period of one year, and may be renewed for one additional year, with salary stipend of $4,000 to $4,800. Facilities are available for housing and maintenance on the grounds, and these facilities can accommodate wives, but not children. Correspondence should be addressed to Max Harry Weil, M.D., Ph.D., Chief, or Morse J. Shapiro, M.D., Senior Consultant, Section of Cardiology, City of Hope Medical Center, Duarte, Calif.

THE FIRST ANNUAL SYMPOSIUM ON CINEFLUOROGRAPHY, sponsored by the Department of Radiology of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y., will be held on Friday and Saturday, Nov. 14 and 15, 1958 (just prior to the Annual Meeting of The Radiologic Society of North America, which begins on Sunday, Nov. 16).

Dr. George H. Ramsey and Dr. James S. Watson, Jr., will be the general chairmen of the Symposium, Dr. Theodore A. Tristan, program chairman, and Dr. Lee B. Lusted, in charge of local arrangements.

The program will include: First day: Cinefluorographic equipment and technique; appraisal of image intensification apparatus, film emulsions and film sizes, processing, viewing and interpretation; radiation dose problems. Second day: Clinical application with detailed consideration of a major organ system. Details of the program and local arrangements will appear in the near future.

All inquiries concerning the Symposium should be addressed to Dr. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N. Y.